SPECIAL EDITION

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The Science of STAYING YOUNG

- Why We Age
- Slowing the Biological Clock
- An Antiaging Pill?
- Replacement Parts
- Attacking Alzheimer's
- Untangling Cancer's Roots

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letter from the editor

The Challenges of Longevity

IT STARTED about a hundred years ago. As improved health care, sanitation and nutrition became more available, we began to make dramatic strides in thwarting the forces that had traditionally shortened human existence. In 1900 some 10 million to 17 million people were aged 65 or older, and they made up less than 1 percent of the world's population. Survival rates began to climb for infants, children and women of childbearing age, gradually lifting humanity's average life span. By 2000, 606 million were aged 60 or older, and they made up almost 10 percent of the world's population. According to the United Nations report *World Population Prospects,* by 2050 that group could swell to 1.9 billion and constitute *one fifth* of the world's projected population. The fastest-growing segment is the so-called oldest old, those aged 80 and above. In 2000, 69 million people were in that category, and in 2050 their number could reach 377 million.

LONGER LIVES are only the beginning.

ED KASHI

But it is not enough simply to live longer. Merely accruing additional years beyond the biblical span of three score and 10 would be unwelcome if they just prolonged suffering from illness and infirmity. No, we want to live better, more youthful days while we're living longer. Diet, exercise and a lucky draw from the gene pool can take us only so far, however. That's where science comes in. In this special edition from *Scientific American,* you'll find firsthand reports from the researchers leading the efforts to understand the mechanisms of aging. They are teasing out ways to slow the biological clock as well as the degradation that time imposes on our bodies and minds. They are battling the diseases of age, including cancer and heart disease.

As medicine grapples with the means to extend life, culture and its institutions will have to wrestle with the consequences of success. Age-entitlement programs, such as Social Security, were formed when younger workers far outnumbered retirees, who drew benefits for only a few years; what reforms will longer lives necessitate? How will families change when siblings can continue squabbling into their 90s? Or when savings and equity are exhausted by parents who may be retired for up to one third of their lives? And, equally important, how will we make our extra years emotionally rewarding and rich?

Medicine will continue to advance, and, we expect, society and policymakers will have to learn to adapt to the challenges of longevity—both providing it and providing for it—that await us all.

Mariette DiChristina
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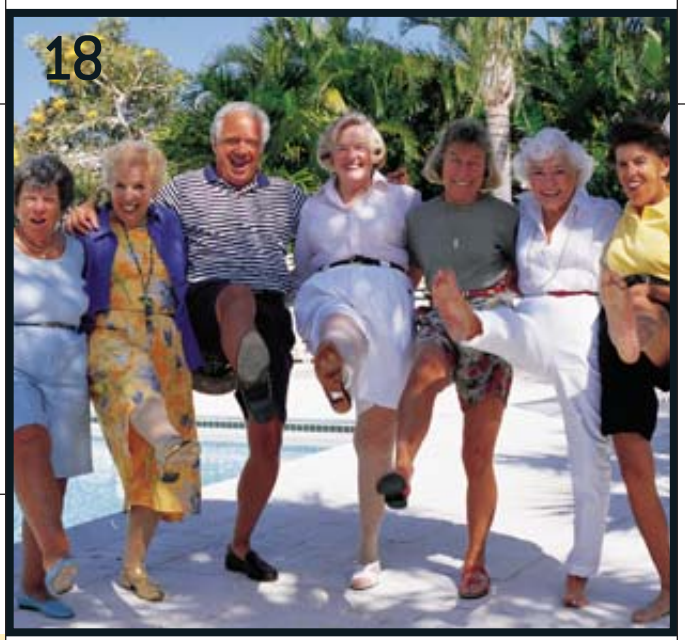

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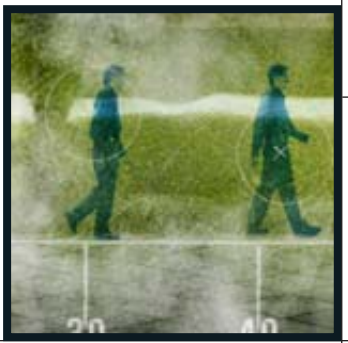

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Cover illustration by Slim Films.

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THE *oldest* old

People in their late 90s or older are often healthier and more robust than those 20 years younger. Traditional views of aging may need rethinking

By Thomas T. Perls

In medical school I was taught that the incidence of chronic, disabling disorders, particularly Alzheimer's disease, increases inexorably with age. I therefore expected that people older than 95 years, often called the oldest old, would be my most debilitated patients. Yet when I became a fellow in geriatrics, I was surprised to find that the oldest old were often the most healthy and agile of the senior people under my care. In fact, the morning I was scheduled to interview a 100-year-old man as part of a research project, he told me we would have to delay the visit. He had seen 19 American presidents take office, and he would be busy that morning voting for the next one.

Such encounters made me wonder if the prevailing view of aging as advancing infirmity was partly wrong. Could it be that many people in their upper 90s enjoy good health and that the oldest old constitute a special—and long-misunderstood—population? Since then, the centenarians I have met have, with few exceptions, reported that their 90s were essentially problem-free. As nonagenarians, many were employed, sexually active and enjoyed the outdoors and the arts. They basically carried on as if age were not an issue. And accumulating evidence indicates that a significant number of the oldest old are indeed healthier than many people in their 80s or early 90s. The common idea that advancing age inevitably leads to extreme deterioration does, indeed, seem to require revision.

Estimated costs of caring for the oldest old in the future might need modification as well. The centenarian population grew by 80 percent in the U.S. during the 1990s. Many demographers predict that 20 million to 40 million people will be aged 85 or older in the year 2040 and that 500,000 to four million will be centenarians in 2050. The economic burden of caring for people older than 85 could be vast, especially if a huge percentage of them need special care. Yet it may well be that health bills for the oldest old will be lower than previously expected.

Some of the first evidence supporting my suspicions came from a study on Alzheimer's disease that I conducted with my mentor, Lewis A. Lipsitz of the Hebrew Rehabilitation Center for Aged in Boston. Surveys reported that this disorder devastates the mind and ultimately kills about 40 percent of those aged 85 and older. Some investigators believe that close to 50 percent of 90-year-olds have Alzheimer's disease and that up to 70 percent of centenarians are affected. Many of the studies on which these conclusions are based, however, did not include subjects older than 93 years, which casts some doubt on these projections. In 1991 Lipsitz and I undertook a pilot study to determine if the occurrence of Alzheimer's disease at the center, a chronic care hospital, matched the predictions for centenarians. We found that of the 12 residents in their 100s, only four seemed to have Alzheimer's disease. This low

Updated from the January 1995 issue

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JOHN R. McCUTCHEN *San Diego Union-Tribune*

100 YEARS OLD AND SWIMMING STRONGLY, Tom Lane raced in the 100-meter backstroke event at the 1994 Senior Olympics in San Diego. Lane was among the many healthy centenarians who contradict the traditional idea that age always brings with it severe debilitation. In addition to swimming, Lane also threw the javelin and shot put and played golf.

figure—only 33 percent—was particularly striking considering that residents of such facilities are more likely to be impaired than are their counterparts in the community.

Selective Survival

OUR FINDING SUGGESTED that, at least cognitively, the oldest old were indeed in better shape than has usually been assumed. What, we wondered, could explain their good condition? We suspect that the answer to this riddle is that, for whatever reason, some people are particularly resistant to acquiring the disorders that disable and kill most people before age 90. Because of this resistance, they not only outlive others, they do so relatively free of disabilities. In a kind of survival-of-the-fittest phenomenon, these individuals seem to be selected for long-term survival because they possess traits that enable them to avoid or delay the diseases that commonly accompany aging. And if they do incur illnesses, they are better able to deal with them.

The concept of selective survival was applied, somewhat more narrowly, by demographers in the 1970s to older African-American populations. Researchers reported that although the death rates for blacks were higher than for whites in the U.S. up to age 75, the trend reversed after that age. Then, in what some called a crossover phenomenon, whites were more likely to die at a given age than were their African-American counterparts. They speculated that blacks tended to die earlier because more of them were economically disadvantaged and had less access to health care services. Therefore, those who survived represented an unusually vigorous group, able to overcome obstacles that defeated others. Their vigor, in turn, later gave them a survival advantage.

This selective survival hypothesis may also clarify various other once puzzling findings demonstrating unusually good cognitive and physical health in the oldest old. It seems that men who sur-

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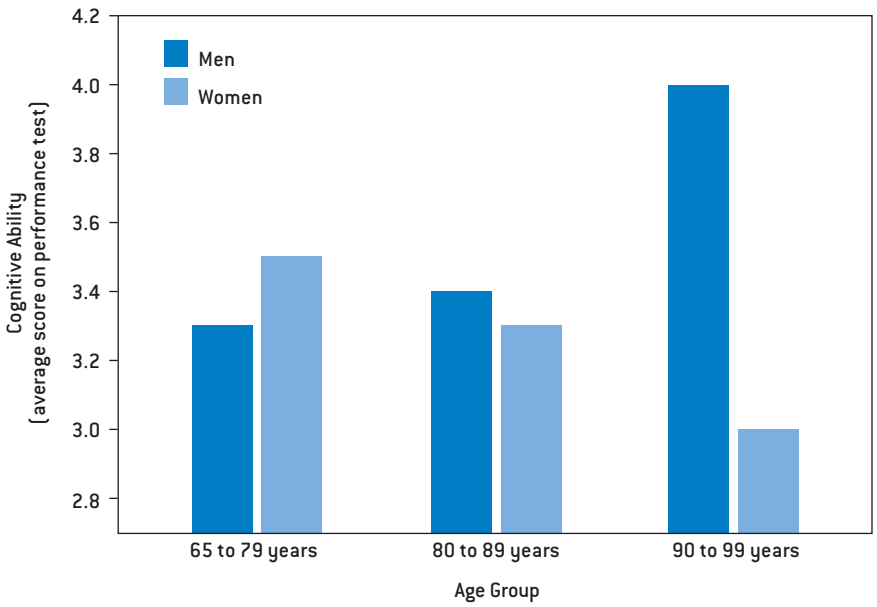
Life Begins at 97

JEANNE CALMENT, a Frenchwoman who lived to age 122, died in 1997. She survived longer than anyone whose age has been confirmed. Calment is among the people who taught researchers that mortality rates for the oldest old are much lower than would be predicted by extrapolating from the death rates of younger individuals (*left graph on opposite page*). James W. Vaupel of the Max Planck Institute for Demographic Research in Rostock, Germany, Anatoli Yashin, now at Duke University, A. Roger Thatcher, formerly of the Office of Population Censuses and Surveys in London, and Vaino Kannisto, formerly of the United Nations, examined death statistics for eight million people. They found that after age 97 a person's chance of dying at a given age veers from the expected trend (*light green*). Instead of increasing exponentially, the rate slows to become more linear (*dark green*). (The ratio would exceed 1 if an entire age group were to die in less than a year.) These findings support the author's suggestion that the oldest members of our species tend to be healthier than expected.

Similar mortality trends were observed among medflies (*right graph*). James R. Carey of the University of California at Davis compared expected death rates (*light orange*) with observed rates (*dark orange*). He found that the chance of dying at any given age peaked at around the age of 50 days. After that, risk declined, so by the age of 100 days, the oldest insects had only a 5 percent chance of dying on a given day.

RECORD HOLDER at her 116th birthday party.

vive into their late 90s become less and less likely to develop Alzheimer's disease with each passing year. Moreover, the average man in his late 90s has a more intact mind than the average man in his 80s. These patterns probably emerge because men who are susceptible to Alzheimer's disease generally die of the condition in their 80s or early 90s. These trends would be explained if the group of men who reach their late 90s consist almost exclusively of individuals who are not susceptible to Alzheimer's disease and who therefore retain their cognitive abilities indefinitely. More study should reveal whether this is the case.



COGNITIVE ABILITIES of oldest old men (*dark blue bar at far right*) are on average higher than the abilities of their female peers even though among people aged 65 to 79, women seem to have a slight advantage. The reversal, known as a gender crossover, occurs between the ages of 80 and 89. It arises because men who are cognitively impaired generally die earlier than do women, leaving mainly mentally intact men who live on.

Gender Crossover

SURPRISINGLY, AS A GROUP, men older than 90 generally have better mental function than do their female peers. Women with dementia, it seems, tend to live with their illness rather than die from it. In consequence, very old women on average retain less of their mental abilities than do men of the same age—who represent the healthy survivors left after other men susceptible to dementia have died off.

At later ages, men also do better than women in terms of physical health. Men in their 60s and 70s are more susceptible than are women to strokes and heart attacks. Delayed onset of these acute conditions allows women to survive longer than men. In absolute numbers, many more women are still alive at 95, but in terms of average mental and physical health, men begin to take the lead. The healthy men who have generally avoided illnesses demonstrate a survival advantage over women: although men make up 15 percent of 100-year-olds, 40 percent of 105-year-olds are male. This switch to more mentally and physically fit men after age 90 could be called a gender crossover.

Early signs of the gender crossover can be seen in studies of 80-year-olds.

GEORGES GOBET *Agence France Presse (top)*; LISA BURNETT (*bottom*)

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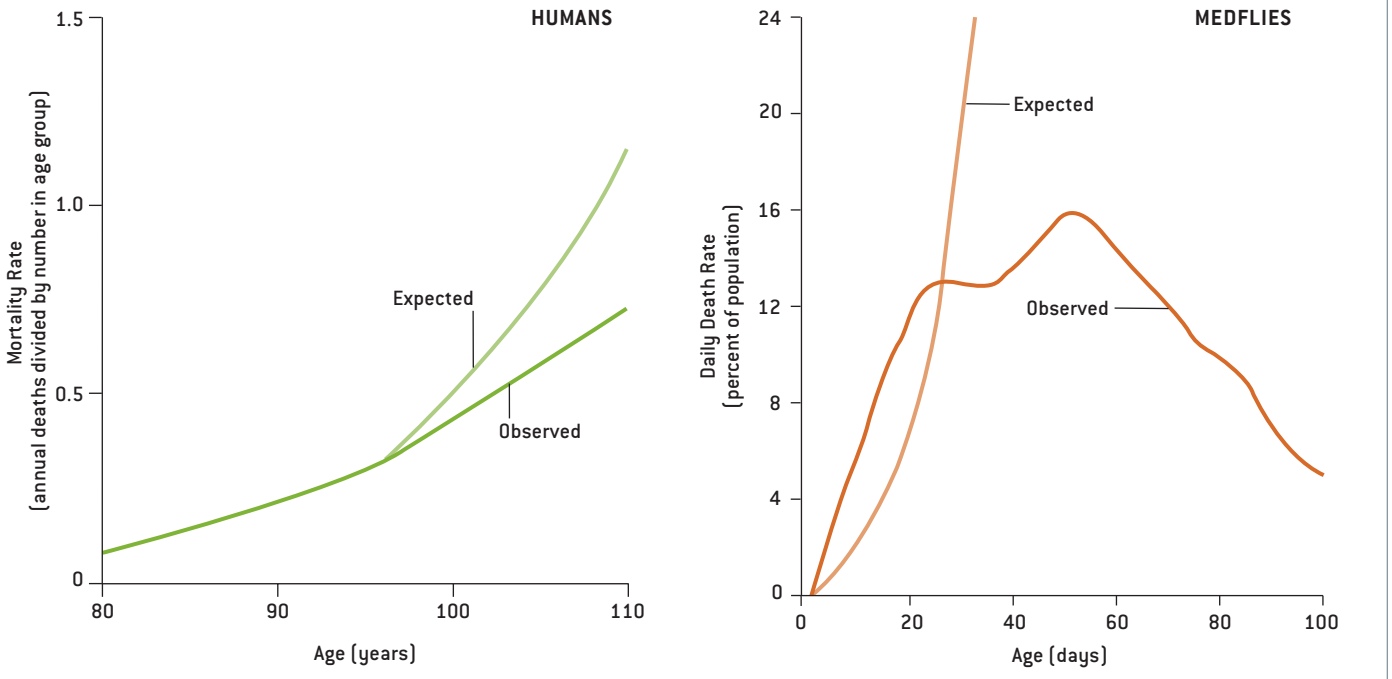

Men who survive to this age without major health problems often continue to live without needing special care. Richard M. Suzman and his colleagues at the National Institute on Aging found that men older than 80 years in one such study were more independent than were similarly aged women. Their report indicated that 44 percent of the men in that age group were robust and independent compared with only 28 percent of women. Additionally, Kenneth G. Manton and Eric Stallard of Duke University estimated the active life expectancy—that is, the years of independent life left—for members of the U.S. senior population. Their findings showed that after age 85, men could expect to live a healthy and active life longer than women could.

What biological and environmental factors might allow the oldest old humans to reach age 95 and beyond in good health? Multiple and intertwined influences undoubtedly play important roles. So-called longevity genes seem to protect against the development of diseases; genetically or otherwise determined adaptive abilities enable survivors to avoid potentially life-threatening conditions. Modifications in everyday activities, such as not smoking, practicing better nutrition and exercising, may also help some people stay fit longer. Basic good luck surely helps as well.

The Genetic Factor

TEMPTING CANDIDATES for possible longevity genes in humans are ones that control the body's mechanism for protecting itself against oxygen radicals. These naturally occurring, highly reactive compounds damage DNA and can destroy cells. Everyone has a genetically determined ability to combat this type of damage. Gene variants that give rise to unusually efficient resistance to oxidative damage could well contribute to the life span of the oldest old by slowing the rate at which oxygen radicals damage cells.

In addition to carrying longevity genes, the oldest old may have an unusually low complement of deleterious genes. For example, one variant of the gene coding for the protein apolipoprotein E (apo-E) has been tied to a substantially increased risk of acquiring Alzheimer's disease. The average age of onset for Alzheimer's disease appears to be related to the type of apo-E genes a person inherits from each parent. There are three common forms: *E2*, *E3* and *E4*. People who inherit two *E4* genes (one from each parent) have eight times as great a risk as the general population of developing the disease; those with two *E4* genes who acquire the disease display symptoms at an average age of 68. Alzheimer's disease patients with two *E3* genes demonstrate symptoms of the disease somewhat later, at about 75 years. The role of *E2* remains unclear, but there is evidence that it is associated with a lower risk of developing Alzheimer's disease.

In collaboration with Bradley T. Hyman's laboratory at Massachusetts General Hospital, we determined the prevalence of *E4* among healthy subjects aged 90 to 103. Our study revealed that 14 percent of the group (with an average

THE AUTHOR

THOMAS T. PERLS met his first centenarian in his own family: his great-grandmother, Julia Grunewald, lived to be 102. As principal investigator of the New England Centenarian Study, Perls has examined definitions of normal aging and pursued preventive strategies for Alzheimer's disease. He received his medical degree from the University of Rochester and his master's in public health from Harvard University. Perls is an associate professor of medicine at Boston University School of Medicine and a geriatrician at Boston Medical Center.

LISA BURNETT

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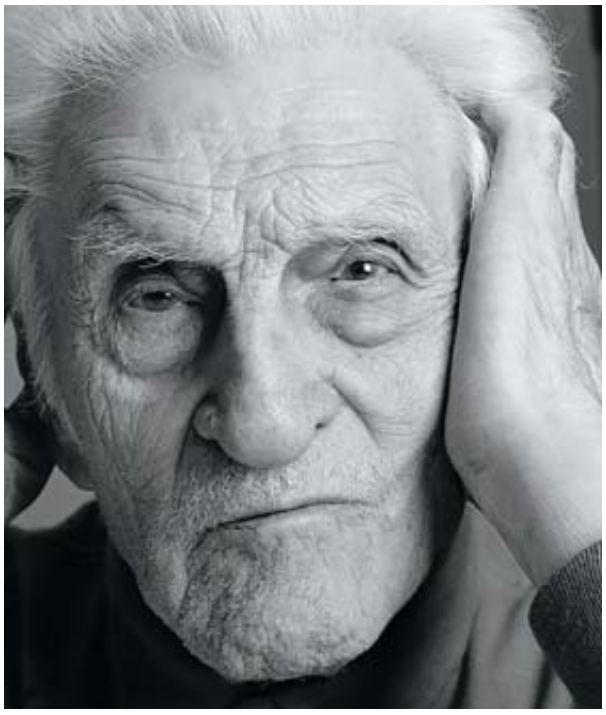
THREE WHO THRIVED

A Little Port Wine Every Day

RESEARCH SUGGESTS that good genes probably provide the best hope for a long and healthy life. Other factors may be important, however. The people shown here had their own hypotheses to explain their longevity; further scientific studies should help clarify the issue.

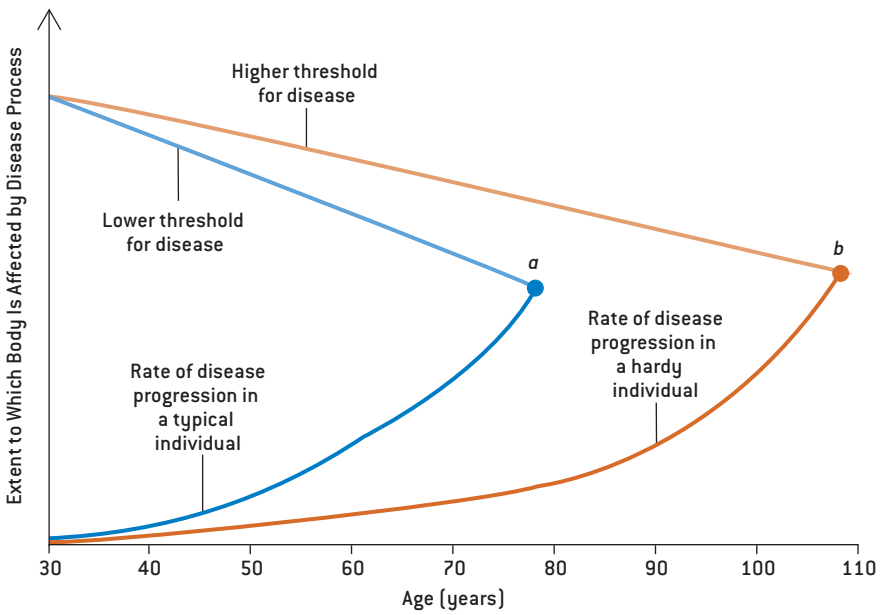


ALFRED BENEDETTI at age 101. He participated in the javelin, shot put and basketball free-throw events in the Senior Olympics from age 90 and went bowling twice a week. Benedetti attributed his health and longevity to abstaining from smoking and drinking—except for two inches of port wine every day. He stayed busy with reading, writing, and working with his hands.

age of 93) had at least one *E4* gene. Previous studies of 85-year-olds indicated that 18 percent carried at least one *E4* gene, and 25 percent of subjects younger than 65 carried the gene type. The occurrence of the *E4* variant decreases markedly with advancing age, dropping nearly 50 percent over 28 years. (Other studies indicated there was an even greater decrease among centenarians.) We suspect that the oldest old groups demonstrate unusually low frequencies of the *E4* gene in part because this gene type is associated with an increased likelihood of developing Alzheimer's disease and dying from it; consequently, many of those with *E4* do not generally survive into their 90s. Although *E4* may be one of many potential markers of increased mortality risk, its value as a predictor of Alzheimer's disease has not been proved.

Genes may provide the blueprint for how long a person might live. In effect, they can be considered indicators of how well a person can cope with disease. As such, genes help to determine two interrelated properties that influence aging: adaptive capacity and functional reserve. Adaptive capacity is a person's ability to overcome a disease or injury or to cope with such stresses effectively. Functional reserve refers to how much of an organ is required for its adequate performance. Obviously, one's adaptive capacity depends in part on the body's functional reserve, because the ability to deal with disease requires the proper functioning of organs.

The importance of these two characteristics to the survival of many oldest



HIGH THRESHOLD for acquiring chronic diseases and a slower aging process may help explain why the oldest old often survive in good health, according to the author's theoretical model. In most people, tissue damage resulting from disease processes occurs relatively rapidly (*dark blue*). Also, their disease threshold becomes lower quickly with age (*light blue*), so the symptoms of age-related diseases appear by about age 80 (*a*). Hardy individuals who age slowly (*dark orange*) and have a higher threshold for disease (*light orange*) become symptomatic much later (*b*), if at all.

ERIK LEIGH SIMMONS (*top left and center*); VICTORIA ENGER *MSU News Service* (*top right*); LISA BURNETT (*bottom*)

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ANGELINA STRANDEL at age 101. She advised, "Watch your calories and keep away from greasy food." Strandel also indicated that although she dealt with much turmoil in her life, she did not let the stress get to her. Strandel's sister lived to age 100.

HERBERT KIRK graduated at age 97 from Montana State University with a bachelor's degree in art. He is shown here with his senior-thesis sculpture project. Kirk attributed his longevity to exercise. When he was 95, he won two gold medals (in 800-meter and five-kilometer races) and one silver medal (in a 200-meter race) at an international seniors' track meet in Helsinki, Finland.

old can be seen in the varying effects that the buildup of neurofibrillary tangles has on cognition. Neurofibrillary tangles describe the web of dead brain cells that occur naturally with aging but appear in abundance in patients with Alzheimer's disease. The number of tangles that can accumulate before signs of Alzheimer's disease emerge varies. For example, an autopsy revealed that a 103-year-old man who displayed few outward signs of Alzheimer's disease had a level of neurofibrillary tangles that in a younger brain would indicate the patient was probably demented. Presumably, the older man had an excess reserve of brain function that allowed him to compensate for the process that was damaging his brain. Perhaps people who have a slow buildup of tangles and a high tolerance for them can remain mentally intact for a long time, showing overt signs of Alzheimer's disease only very late in life, if at all.

New Thoughts on Aging

THE DISCOVERY that many people older than 95 are in good shape may mean that future planning for the health care of the oldest old will need to be revised. Much of that planning is based on the theory that although lethal conditions might be postponed as medical technology improves, the incidence of degenerative diseases will be unaltered. The theory predicts that the oldest old will keep suffering from more disease and chronic disability than do people in their 80s. If this theory were true, then the continued increase in the size of the oldest old population would portend a significant burden of poor health and quality of life among the oldest members of our society.

The emerging data, however, fit better with an opposing theory. James F. Fries of Stanford University has proposed that better ways of life and medical advances will compress morbidity, mortality and disability into a shorter time period. Thus, the onset both of major fatal diseases (heart disease, cancer, stroke and Alzheimer's disease) and of age-associated debilitating diseases (degenerative joint disease, sensory impairments and benign memory loss) would be postponed.

Consistent with Fries's hypothesis, robust centenarians often have a relatively short period of infirmity before death. Although cause-of-death statistics for centenarians are sparse, available information suggests that the usual causes are acute illnesses such as pneumonia, as opposed to long-standing lethal conditions. In some ways, then, the oldest old resemble Fries's image of the future; perhaps they represent the rare individuals who can already resist disease on their own, without the help of advanced medical science.

Madame Jeanne Calment of Arles, France, died at age 122 in August 1997, making her the longest living person ever. Most of us with Methuselean aspirations, in contrast, are up against incredible odds. But recent research on the oldest old has prompted new thinking about the biology of aging. Genetic, biochemical and epidemiological studies should reveal exactly why some people possess resistance to debilitating conditions—and may offer ways to increase that ability in a broader swath of the population. Further, to our relief, the research implies that as the oldest old become more numerous, they may not become a massive drain on the economy. Counter to prevalent theories of aging, many people in their late 90s or 100s lead active, healthy lives. If they represent a "survival of the fittest" cohort, the time may have come to abandon our past perceptions of our oldest citizens. SA

MORE TO EXPLORE

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IMMORTALITY MAY NOT BE IN THE CARDS, BUT WORMS, FLIES AND PIGEONS MAY BE ABLE TO TEACH US A THING OR TWO ABOUT LIVING BETTER LONGER

making methuselah

BY KAREN HOPKIN

CYNTHIA TURNER

IS A FOUNTAIN OF YOUTH in your future? By elucidating the factors that drive the aging process, researchers are hoping one day to postpone the inevitable ravages of age—and perhaps prolong life.

"Most people are interested in living long and fruitful lives," begins the TV talk-show host, glancing at his notes.

"Fruit is good," interrupts the 2000-Year-Old Man. "Fruit kept me going for 140 years once when I was on a very strict diet. Mainly nectarines. I love that fruit. Half a peach, half a plum. It's a hell of a fruit."

In their classic 1950s comedy routine, Carl Reiner and Mel Brooks had at least part of it figured out: we all want to live long and fruitful lives. But the answer may not lie in nectarines.

It may lie in worms. Or, more specifically, in what scientists are learning about longevity as they study organisms as diverse as roundworms, fruit flies, monkeys and humans. Their findings lend hope to those who think we might someday be able to slow the process of human aging. "We can markedly increase the life span of simple organisms," reports Judith Campisi of Lawrence Berkeley National Laboratory. Researchers have found mutant worms, for example, that live up to 120 days—that's about six times their normal life span and the equivalent of 500 years for you and me. They have also discovered treatments that can make normal human or animal cells grown in dishes live forever. And they have developed diet regimens that can increase life span while making animals healthier (though not necessarily happier).

"We're undergoing a major scientific revolution in our understanding of aging," maintains Michael R. Rose of the University of California at Irvine. But will any of these developments translate into a sip from the fountain of youth? Will scientists ever come up with a pill to keep you looking good and feeling fine into the triple digits? Or forever?

Questions such as these capture the imagination—and spark heated debate. "Our studies suggest that the rate at which animals age is not fixed in stone," states Cynthia Kenyon of the University of California at San Francisco. Kenyon has identified mutations that vastly increase the life span of roundworms. "By changing a few genes," she continues, "we can outwit death and keep the worms alive and youthful much longer." Simply mutating genes that control how these worms respond to hormones that resemble insulin, for instance, enables them to live two to six times as long. A treatment that produced similar results might work for people, too. "If we can make it to 90," she surmises, "I see no reason why, in principle, we couldn't make it to twice that."

Other scientists are less optimistic, though. "Such gene manipulations merely postpone the initiation of the aging process," declares U.C.S.F.'s Leonard Hayflick. "Aging is inevitable. Everything ages, including the universe." In 1961 Hayflick discovered that normal human cells, when grown in a culture dish, divide a limited number of times (about 50) and then die. This ultimate ceiling has been dubbed the Hayflick limit. "Saying that in 20 years we'll all live to be 200 is utter nonsense," Hayflick contends.

The Triumph of Entropy

FIRST OFF, there's a difference between life span and life expectancy. Life expectancy, the number that appears on an insurance company actuarial table, reflects the average number of years a person can expect to live. Life span represents maximum longevity—the absolute number of years any hu-

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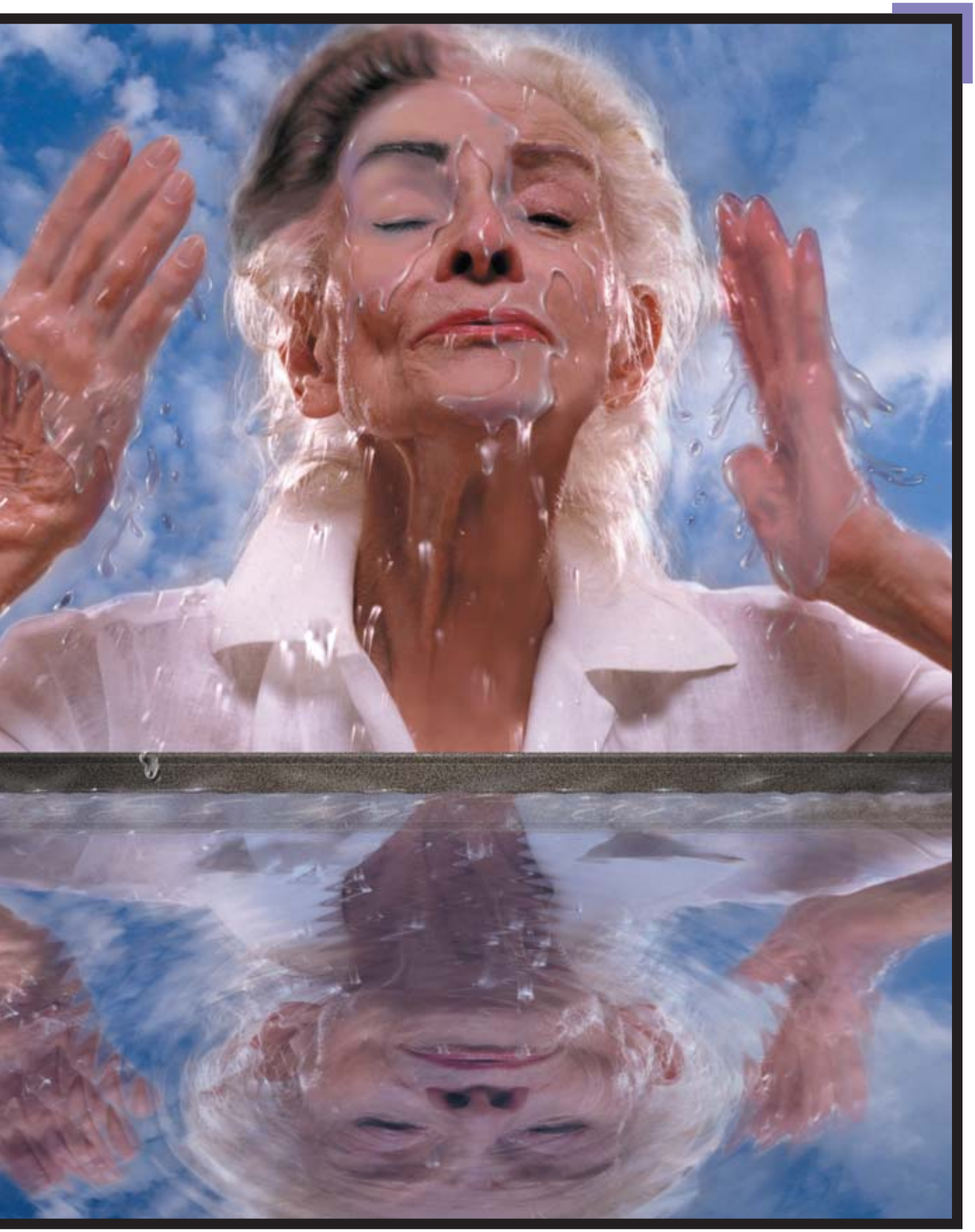

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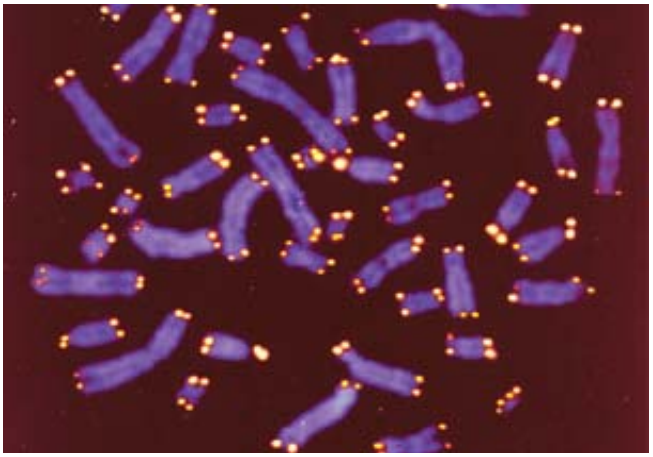

TELOMERES, which show up as glowing caps on the chromosomes above, may be the molecular timekeepers of the body. Each time a cell divides, its telomeres get a little shorter; at a crucial limit, the cell may die.

man could hope to survive. The good news is that life expectancy has been on the rise for some time. People now live into their 70s, on average, which wasn't always the case. "99.99999 percent of the time humans have inhabited this planet, our life expectancy at birth has been no more than 18 to 20 years," Hayflick notes. The increase we enjoy now is largely the result of humankind conquering many infectious diseases and developing basic hygienic innovations such as clean water, sanitation, soap and refrigeration. What is more, studies show that we're living not only longer but healthier, according to Richard J. Hodes, director of the National Institutes of Health's National Institute on Aging. As a population, we are less plagued than ever before by physical infirmity, muscle wasting, osteoporosis and the like.

But how old can we possibly live to be? It's hard to predict, says Leonard P. Guarente of the Massachusetts Institute of Technology and co-founder of Elixir Pharmaceuticals, which is searching for drugs that might mimic the effect of genes that extend longevity in yeast and worms. "If we extend life span even a few years," he says, "cancer will kill everybody." And even if we duck cancer, he continues, wear and tear will weaken our veins and arteries, and our organs will eventually have to be patched up or replaced.

Even eliminating the diseases that now kill us would not increase our life expectancy substantially, Hayflick argues. Cure heart disease, add a dozen years; cancer, two or three more, he claims. "So if you cured both tomorrow morning, you'd only increase life expectancy by another 15 years. That's it, period. End of sentence." Hayflick believes that the human life span may be fixed by our genes at an upper limit of about 125 years.

Our maximum life span may have become set during evolution, because there is really no need for any creature to live beyond its reproductive years. By the time an animal bears children, it has fulfilled its biological destiny to pass on its genes and is just taking up space and sponging off its kids. Humans escape this seemingly cruel contract, generally speaking, because we have no natural predators.

In any case, evolutionarily speaking, there must be a price to be paid for longevity, suggests Steven Austad of the University of Idaho, who studies aging in wild mice, opossums and birds. "Otherwise we'd all be long-lived."

But maybe we only make that argument because we're one of the longest-lived animals around, Kenyon counters. "If we were dogs, we'd look at humans and think, 'Hey, they live for a really long time, why can't we?'" Even if natural selection did not favor the evolution of humans with the longest life spans, Hodes declares, "there's no reason why we can't change that." But to come up with potential therapies to slow or halt aging, we first need to understand why we age.

Beginning at the End

BY NOW ALMOST EVERYONE has heard of telomeres—the bits of repetitive DNA sequences that cap and protect the ends of our chromosomes. Even the border guard who checked Kenyon's passport as she crossed into Canada to attend a conference on aging emitted a knowing "Ah, telomeres" when she described the purpose of her visit. But how do telomeres relate to aging?

There's no doubt that telomeres are important for keeping cells alive in culture dishes in a laboratory. Allow connective tissue cells called fibroblasts to grow in culture, and their telomeres get shorter and shorter each time the cells divide. And when a cell's telomeres shorten enough, they signal the cell to stop dividing. Activate telomerase—an enzyme that rebuilds telomeres—and cultured cells become immortal. Cancer cells can keep dividing in part because they reactivate their telomerase.

But is telomere shortening involved in aging in the body? It's debatable. In the body, telomeres do dwindle in size as cells age, eventually shrinking to a length that would signal the same cells to stop dividing in a culture dish.

WHAT A DIFFERENCE a gene makes. An elderly, two-week-old nematode worm (*left*) is sluggish and stiff compared with a two-day-old adult (*center*). In contrast, a mutant worm (*right*) lacking a gene for responding to hormonal signals continues to look youthful, even at two weeks.

COURTESY OF GERON CORPORATION (*top*); CYNTHIA KENYON, DELIA GARIGAN AND JAVIER APFELD *University of California, San Francisco* (*bottom*)

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But there's no direct evidence that human cells stop growing in the body because their telomeres are too short, Guarente points out. "Cells from old people grow just fine in culture," he says. And as far as we know, Austad adds, "animals don't typically die because their cells don't divide any longer."

Still, researchers who earn their living studying telomeres are hedging their bets. "It's simply too early to judge," asserts Titia de Lange of the Rockefeller University. "We just do not know enough about telomeres and aging in humans."

That's where the mice come in. To examine more directly the link between telomeres and aging, Ronald A. DePinho of the Dana-Farber Cancer Institute in Boston has generated mice that lack telomerase and found that as these animals age their telomeres shrink. They also go gray and lose their hair—a result that de Lange deems "remarkable." The rodents do not, however, develop many of the other maladies generally considered hallmarks of aging, such as cataracts, osteoporosis and cardiac disease. DePinho's conclusion: "Telomere shortening is not the cause of overall aging as we know it."

But certain cells or tissues—especially those that are dividing rapidly—probably do become crippled by shortened telomeres, suggests Calvin B. Harley of Geron Corporation in Menlo Park, Calif. Withered telomeres might help weaken the immune system, bones or skin, for example, all of which contain rapidly dividing cells and all of which are compromised as we age. In these cells, telomere shrinkage may reach a critical point, after which chromosomes begin to break. So someday doctors might boost immune function or strengthen bone or skin by turning on telomerase in the appropriate cells. Telomerase might also help extend the lives of the rapidly dividing endothelial cells that line blood vessels, allowing them to repair the wear and tear caused by a lifetime of vigorous blood flow.

But would switching on telomerase in every cell in the body allow people to live to the ripe old age of 150? "I doubt it," Harley says. "When it comes to maximum human life span, so many other factors could be involved."

Oxygen: A Deadly Gas

FREE RADICALS are one example. Scientists have hypothesized since the 1950s that destructive molecules called free radicals might contribute to aging. These oxygen molecules—which are generated as by-products as cells convert food into energy—can damage almost every critical component of cells, including DNA, proteins, and the fatty compounds that make up the inner and outer membranes.

"Oxygen is toxic," asserts Rajindar Sohal of the University of Southern California. And the rate at which an animal ages may relate to how well it detoxifies oxygen radicals. Sohal has found that aged flies accumulate specific types of free-radical damage in their mitochondria—the tiny subcellular organelles that provide power to cells and tissues, including a fly's flight muscles. Further, Irvine's Rose has bred flies that live more than twice as long as normal. He finds that they show, among other things, an increase in the activity of superoxide dismutase (SOD)—an enzyme that destroys toxic oxygen radicals called superoxides.

Free radicals might also explain why pigeons live 35 years, 12 times as long as rats, animals that are about the same size. For the amount of oxygen they take in, pigeons produce half as many free radicals as rodents do. Perhaps we should be studying these animals to see how nature solves the aging problem, Austad suggests.

Along the way, researchers need to be mindful of whether they are seeing cause and effect or simply a correlation, Guarente warns. Sure, oxygen radicals and cellular damage increase with age. But just because antioxidants increase life expectancy does not mean that free radicals cause aging. Banning motor vehicles would increase our life expectancy by about six months, Hayflick notes, "but that doesn't mean cars cause aging." Free radicals can't be the bottom line when it comes to aging, agrees Campisi of Lawrence Berkeley National Laboratory: "Mice and men live in the same toxic world."

So is SOD therapy likely in our future? "There's no guarantee it will work in humans," Rose admits. How about taking megadoses of antioxidants, such as vitamins C and E? That may not be good either, cautions Hodes, who recalls a study in which a group of smokers given the antioxidant beta carotene actually developed more cancers than a group of control subjects did.

No Sex + Less Food = Long Life

ARGUABLY THE MOST STRIKING RESULTS of studies examining ways to boost longevity come from investigations of the simplest organisms. Kenyon, for instance, looks at worms that live two, four or six times as long as average. The creatures' longevity seems to boil down to the way they respond to hormones similar to insulin. Like a conductor directing an or-

WHICH MOUSE IS OLDEST? Actually, they're all 39 months, which is beyond elderly in rodent years. The two in the middle look sleek and healthy because they've been maintained on a diet containing half the calories eaten by their scraggly companions. Researchers are trying to find out how such caloric restriction can lead to long life.

RICHARD H. WEINDRUCH *University of Wisconsin–Madison*

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chestra, Kenyon says, insulinlike hormones direct the activity of a suite of genes, including genes for antioxidants such as SOD, genes that regulate metabolism, genes that kill infectious microbes, and genes that help keep cells in good working order. Individually, each of these genes makes a small contribution to longevity. Together they allow the worms to stay frisky and svelte way past their prime.

Interestingly, Kenyon finds that removing the reproductive stem cells that produce the worms' sperm and eggs does the same thing. These stem cells accelerate aging, perhaps by producing hormones that control longevity. Such an arrangement may allow animals that mature slowly to remain healthy long enough to reproduce.

This dovetails nicely with what Rose finds in his flies. He breeds longer-lived flies by delaying when the insects reproduce. "Like 'good' teenagers, they don't waste their energy on sex," he reports. As a result, they have more verve left for later. When these flies are 40 or 50 days old—over the hill in human terms—"they're flying around, fornicating and having a good time while the regular flies are dying," Rose says.

Does that mean people should put off having kids? "Oh, no, that's totally impractical," Rose responds. "What I'm doing to these flies is much more severe than what career women are doing." Besides, delaying parenthood would not affect your own life span—although it might help your descendants live it up 100 generations down the line.

The caveat? Scientists need to be certain that they are not looking at interventions that merely decrease metabolic rate, which also increases life span. Put a fly in the fridge, and it will live eight or nine times as long, Sohal states. But humans probably would not want to live longer if they had to chill out and hibernate. Although Rose's flies appear to have the same metabolic rate as adults, DePinho insists, "we need to bring these findings back to mammalian systems to see how relevant they are." In-

TALKIN' 'BOUT REGENERATION

FORGET THE FOUNTAIN OF YOUTH. Slowing down aging may be less of a priority when we are able simply to replace faulty body parts as they wear out.

Okay, ordering Dad a new liver from Hammacher Schlemmer may not be in your immediate future. But right now biotech companies are placing stock in the idea that researchers and physicians may one day be able to direct the formation of spare body parts—be they bone, liver, pancreas or skin.

To do that, scientists are taking tips from embryos. Cells and organs can be regrown, it stands to reason, with the same molecules that the embryo used to grow them in the first place. It is "unlocking the body's capacity to repair and regenerate," declares Doros Platika, founder and former CEO of Curis in Cambridge, Mass.

Proteins with names as fanciful as Sonic hedgehog, Indian hedgehog and Patched all play an important role in the development of neurons, bone, cartilage, skin and hair. These same molecules, Platika says, can stimulate the growth of the corresponding tissues in an adult. The dream is to get organs to regenerate in place inside the body, not to implant a new part grown on the outside. "It may not be as sexy as a brain pulsing in a dish," Platika admits. But growing organs inside the body is better, he says, because it would allow molecular signals to be delivered in the correct context, directing organs to grow to the proper size and shape and to make the appropriate connections with blood vessels, nerves and other tissues.

CUT OFF A NEWT'S LEG, and it grows back weeks later (and, in this sequence, in a lighter color). Why can't humans regenerate limbs and other body parts the same way?

"I don't think it's complete fantasy," comments Hans-Georg Simon, who studies regeneration in newts at Northwestern University Medical School. "The human body has quite remarkable capabilities for repair and regeneration." The problem is that we tend to lose that capacity as we age.

Very young children can regrow their fingertips—even up to the first knuckle, notes Clifford J. Tabin, a developmental biologist at Harvard Medical School and an adviser to Curis. The trick is not rushing to heal the wound. Forming a scar is a quick and dirty way to prevent infection, but it eliminates the potential for growing new parts.

At least that's what happens in newts. Of course, these tiny creatures are at liberty to burrow into the muck for two months until they grow a new limb. "Chop off any part of a newt, and if the animal survives, it'll grow back," Tabin claims. It appears that adult newts retain something of the embryo's ability to allow all its cells to divide—something humans shut down, probably to avoid the runaway cell division that is characteristic of cancer.

In the next decades, regeneration might allow doctors to repair hearts, livers, skin and even injured spinal cords. But we might think twice about trying to regrow, say, a leg. "It took you 18 years to grow your leg to the size it is today," Tabin observes.

It's not a stretch to think that such techniques could be used to treat some of the disabilities associated with aging, according to Platika. Being able to regrow bone, for example, could save a woman with osteoporosis.

Ultimately, keeping people looking and feeling fit into their old age will be "more important than greatly extending life span," Platika asserts. "We want to be a bunch of gorgeous hunks and babes that are 100 years old."

—K.H.

HANS-GEORG SIMON *Northwestern University Medical School*

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deed, researchers have shown that insulin and insulinlike hormones do have a hand in controlling life span in mammals. Dwarf mice that produce less insulinlike growth factor-1 (IGF-1), a hormone that regulates metabolism and growth, live longer than their standard-size counterparts. And mice that have been engineered to respond poorly to insulin or to IGF-1 live some 20 to 25 percent longer than normal. Because the hormones that influence longevity in worms also work in mice, these systems might affect aging in humans, too, Kenyon says.

Aside from genetic manipulation, the only intervention that so far has been proved to slow aging in mammals is calorie restriction. Mice and rats raised on a diet high in nutrition but reduced in calories by 30 to 60 percent live about 30 to 60 percent longer—and by most measures are healthier to boot, reports Richard H. Weindruch of the University of Wisconsin–Madison. In addition to his work with rodents, Weindruch has been following a colony of rhesus monkeys that have been on a restricted diet for more than 10 years. Compared with nondieting animals, these middle-aged monkeys have low insulin levels and are better able to regulate their glucose. And they have lower triglyceride levels, which means they are probably less prone to developing atherosclerosis, another benefit that might allow them to live longer.

"Saying that in 20 years we'll all live to be 200 is utter nonsense."

The food-restricted monkeys also have less free-radical damage to their skeletal muscles than animals that are allowed to eat their fill. Together these results suggest that the researchers who are finding that insulin regulation and oxygen radicals are important in aging in flies, worms and mice are on to something.

But calorie restriction won't necessarily lead to another new "miracle" diet. "Nobody proposes that we starve people so they live to be 150," Campisi counters. And the truth is that this diet would not be easy for people to pull off, Weindruch admits. It's tricky to cut that many calories and still maintain proper nutrition. But if scientists can catalogue the physiological changes that occur in these animals, they may be able to find a drug that accomplishes the same thing in humans who won't give up their Häagen-Dazs.

David Sinclair, a pathologist at Harvard Medical School, has discovered that a chemical prevalent in red wine mimics the longevity-enhancing effects of calorie restriction in yeast. The compound, called resveratrol, acts by goosing the activity of the "sirtuins," a family of enzymes that Guarente first linked to longevity. The chemical, Sinclair says, also enhances the activity of a sirtuin called SIRT1 in cultured human cells. Whether resveratrol or some other sirtuin-stimulating compound can lengthen life span in mammals is not yet known, but Sinclair has founded a company called Sirtris to hunt for drugs that target SIRT1.

Pill Me

WHAT DOES ALL THIS PRESAGE for potential antiaging therapies? The findings in calorie-restricted mammals suggest that to some degree longevity hinges on hormones such as insulin and IGF-1 that control glucose metabolism, cell growth and body size, notes Richard A. Miller, a pathologist who studies aging mice at the University of Michigan Medical School. And the worm studies reveal that related hormonal pathways might regulate aging in all organisms. Animals that burn glucose more efficiently—extracting more energy from less blood sugar—somehow manage to live longer and healthier lives, Austad adds. This raises the possibility that therapies aimed at manipulating hormones might put the brakes on aging—or perhaps stave off aging-related ills such as osteoporosis, muscle loss, heart disease and cancer.

Still, "there's not going to be a magic bullet" to beat Father Time, Rose predicts. Campisi agrees. "To think that a single pill would slow all aging is extremely naive," she says. But someday certain interventions may be used to help particular systems of the body last longer and to prevent some age-related disorders. Retarding the death of neurons may not dramatically extend life span, for instance, but it might delay the onset of neurodegenerative diseases such as Alzheimer's so that they do not appear until age 90 or 100.

And as with anything, living longer may have its price. So-called dwarf mice, which are about one third the size of normal mice and live 50 to 70 percent longer, are sterile. Calorie restriction delays puberty in rats, mice and monkeys. And the maggots produced by long-lived flies die in greater numbers than those of normal flies do. "So we're never going to see childhood immunization against aging," Austad advises. But therapy later in life, after childbearing, might be an option.

Just beware the quick fix, Miller warns. Most of the people who will tell you that we can prolong the human life span are "quacks who have something to sell." If Austad were less scrupulous, he might be among them. "I like the royal jelly idea," he comments. People eat this gooey substance because bees feed it to their queens and queens live longer than drones, he says. "But mostly it's just bee poop." Perhaps the fact that researchers who study aging aren't getting rich hawking antiaging therapies suggests that they haven't found the answers—yet.

"Right now aging is still very much a black box," Guarente admits. "But we're standing on the brink of understanding." This knowledge might not keep us all frolicking until we're 200, but it should help us stave off disease and remain healthier longer. SA

Karen Hopkin is a freelance science writer based near Boston. She, too, believes in nectarines.

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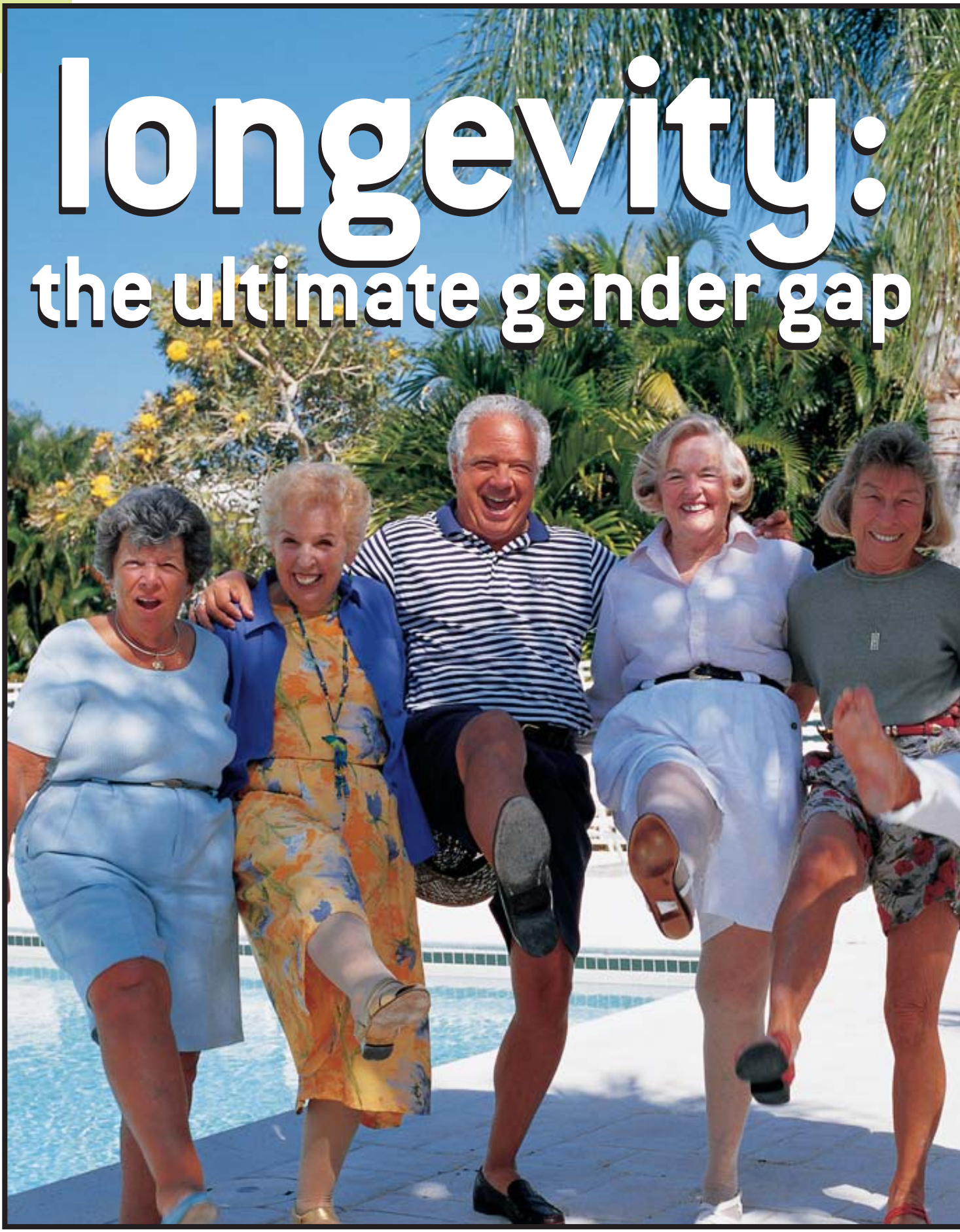
longevity:
the ultimate gender gap



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ELDERLY MEN are greatly outnumbered by elderly women in most retirement communities in the U.S. Women are about 40 percent more likely than men to live to the age of 65 and almost three times more likely to reach 85.

JEFFREY SALTER

AN AMERICAN MAN'S AVERAGE LIFE SPAN IS MORE THAN FIVE YEARS SHORTER THAN A WOMAN'S. DIFFERING HORMONE LEVELS AND LIFESTYLE CHOICES MAY HELP EXPLAIN THE DISPARITY

BY HARVEY B. SIMON

"Why can't a woman be more like a man?" It's a humorous question asked by Professor Henry Higgins in a show-stopping song from the Broadway musical *My Fair Lady*. But Higgins would sing quite a different tune if the subject was longevity. When it comes to life span, why can't a man be more like a woman? Women do indeed live longer than men. But why? And can men do anything to catch up?

Over the past half a century, life expectancy in the U.S. has risen slowly but steadily year after year. The main reasons for this trend are the dramatic advances in medical diagnosis and treatment as well as the changing American lifestyle, with its new emphasis on healthier diets and regular exercise and its declining dependence on tobacco. One thing, though, has not changed: the gender gap in life expectancy. People of both sexes are living longer, but the gains in women's life expectancies have outpaced those of men. In 1930 the average life span for American women was 61.6 years, and the average for men was 58.1 years; by 2002 the average female and male life spans had risen to 79.9 and 74.7 years, respectively. In other words, the gender gap is now 50 percent greater than it was 70 years ago.

It is an impressive difference, and it is responsible for the striking demographic characteristics of older Americans. Half of all women older than 65 are widows, and widows outnumber widowers three to one. At age 65, for every 100 American women, there are only 70 men. At age 85, there are only 38 men for every 100 women. And the longevity gap persists even into very old age. That is why female centenarians outnumber their male counterparts nine to one.

The gender gap is not unique to America. Every country with reliable health statistics reports that women live longer than men; the observation is at least as old as health statistics themselves, because women outlived men by nearly three years when such data were first recorded in Europe more than 200 years ago. The longevity gap is present both in industrial societies (79 versus 73 years in western Europe and Australia) and in developing countries (54 versus 51 years in sub-Saharan Africa). It is a universal phenomenon that suggests a basic biological difference between the aging processes in males and in females.

Doctors are not sure why women live longer, but it is likely that many factors contribute to the gender gap. Males differ from females from the very moment of conception. It's all in the genes: the male Y chromosome begins the process of sexual differentiation in the second trimester of pregnancy, when the fetal testicles secrete the male hormone testosterone. The importance of fetal hormones in determining sex characteristics is obvious, but their role in influencing longevity is far from clear. Still, new research suggests that events during fetal

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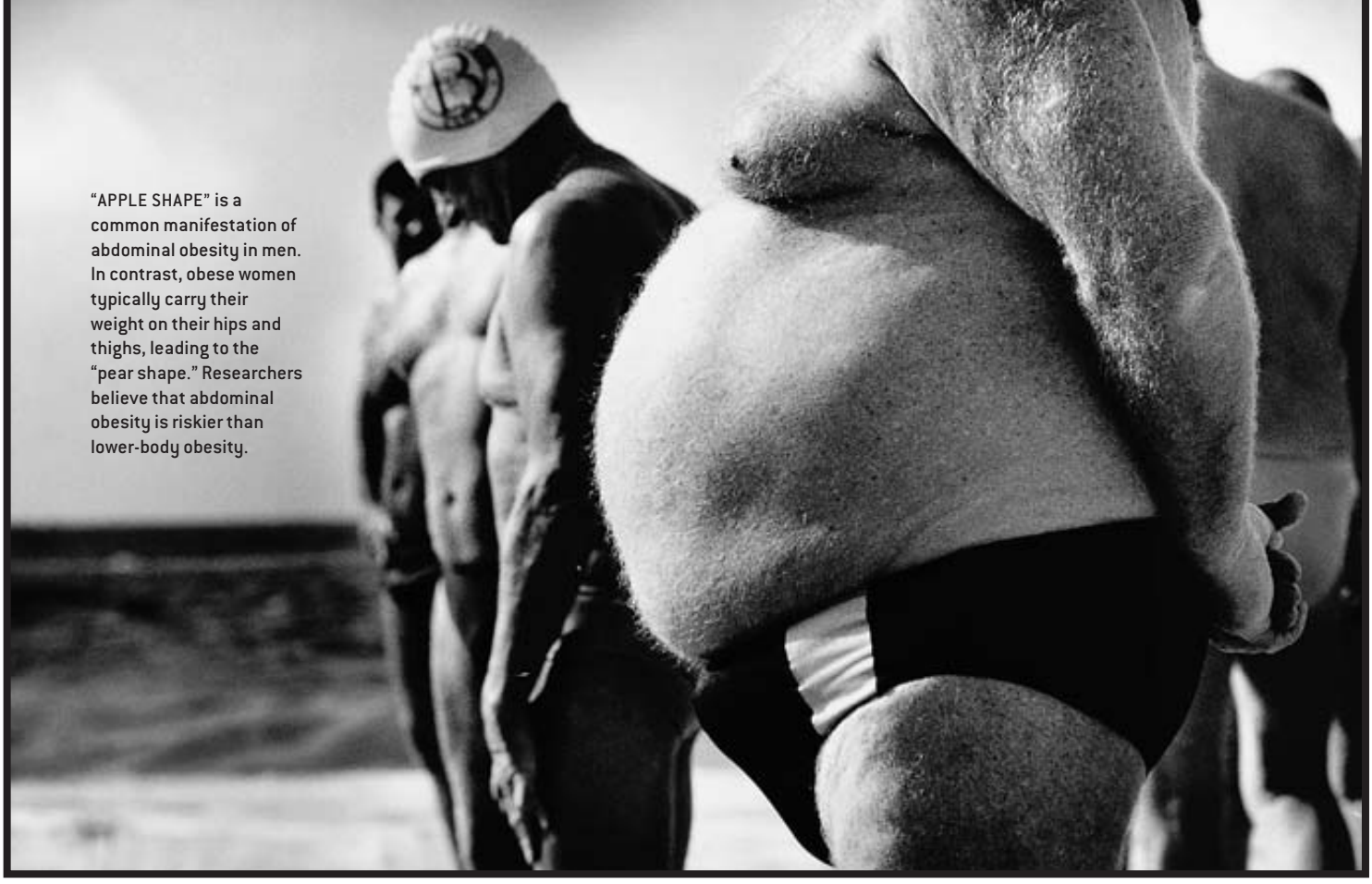

"APPLE SHAPE" is a common manifestation of abdominal obesity in men. In contrast, obese women typically carry their weight on their hips and thighs, leading to the "pear shape." Researchers believe that abdominal obesity is riskier than lower-body obesity.

life can affect health in adulthood. For example, studies have shown that a low birth weight—often caused by poor nutrition during pregnancy—increases a man's risk of heart attack and stroke in adulthood. So it is conceivable that the levels of sex hormones at the very beginning of life also might influence events at the very end of life.

Estrogen and Testosterone

INDEED, the longevity gap makes its first appearance in embryonic life itself. Sperm cells that contain a Y chromosome can outswim sperm bearing an X; as a result, 115 males are conceived for every 100 females. But for reasons that are not entirely understood, male embryos are more likely to miscarry than females, so boys outnumber girls by only 104 to 100 at the time of birth. The excess of male deaths continues in infancy and early childhood, but the difference is small until adolescence, when testosterone kicks in and boys start behaving like men. The results: motor vehicle accidents, homicides and other violent deaths that send the male death rate soaring to three times the female rate between the ages of 15 and 24. By age 25, females outnumber males, and the gender gap keeps widening with each subsequent decade of life.

The difference in estrogen and testosterone levels between men and women is the simplest way to account for the gender gap, although it does not fully explain the variance in life expectancies. During their reproductive years, women are much less likely than men to suffer from heart disease. Estrogen makes the difference: the female hormone lowers LDL ("bad") cholesterol and raises HDL ("good") cholesterol. After menopause, estrogen levels plummet, LDL rises and HDL falls; it's no wonder, then, that heart disease is the leading cause of death in older women as well as in older men. But women who take estrogen after menopause have about 50 percent fewer heart attacks. They benefit, too, from a similar decrease in strokes as well as a reduced risk of colon cancer and possibly Alzheimer's disease. Even without postmenopausal hormone replacement, women have high estrogen levels for the three to four decades between puberty and menopause; that's up to 40 years more than men, and it helps to explain the gender gap.

Estrogen protects women, enhancing their longevity by reducing the risk of heart attack and stroke. Although men have much less estrogen, they have much more testosterone. Produced by the Leydig cells in the testicles, testosterone rises to high levels during fetal life, when it plays a crucial role in the development of the male genital organs. That work done, the hormone falls to low levels by one year of age; it remains low until puberty, when it surges up to the adult range. Testosterone levels remain steady until about age 40, when they begin to drift down. But it is a slow decline that averages only about 1 percent a year, and most men continue to produce sperm cells even when their testosterone levels drop well below their peak.

Testosterone makes the man: the hormone is responsible for the large muscles, strong bones, deep voices and receding hairlines that characterize the gender. It is essential for sperm production and fertility, and it has an important, if not completely understood, role in libido and potency. Testosterone also contributes to the aggressive behavior patterns that typically distinguish men from women. But can testosterone also

GLENN HUNT

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make men ill? The very large doses of androgens (male hormones) that are used illicitly by some athletes certainly are hazardous, frequently causing aberrant behavior, liver tumors, sterility and heart disease. Drug abuse is one thing, natural testosterone another—but new evidence suggests that even the normal levels of testosterone produced by a man's body may increase his risk of suffering a life-shortening disease.

The prostate is an obvious example. In the prostate, testosterone is converted to dihydrotestosterone (DHT), the hormone that causes up to 80 percent of men to develop benign prostatic hyperplasia (BPH) as they age. BPH is well named; it is a benign enlargement that does not usually shorten life, although it often lengthens one's time in the bathroom. (The enlarged prostate squeezes the urethra, which slows the urine stream.) But DHT is also the hormone that drives prostate cancer, the disease that kills about 3 percent of American men.

Testosterone is no friend of the prostate, but its effects on the heart and circulation are more complex. In high doses, the hormone can lower levels of HDL cholesterol. But in physiological doses, testosterone does not have a major effect on blood cholesterol levels. Several small studies hint that testosterone therapy may even improve the flexibility of arteries, enhance blood flow to the heart and boost the pumping ability of a damaged heart. Present data are incomplete and even contradictory, however; more research is needed to determine if testosterone is protective or heart breaking.

Men cannot change their chromosomes, and very few would change their hormones, even in quest of longevity. But men can catch up with women by refraining from some of the lifestyle choices that add to the gender gap.

Smoking and Alcohol

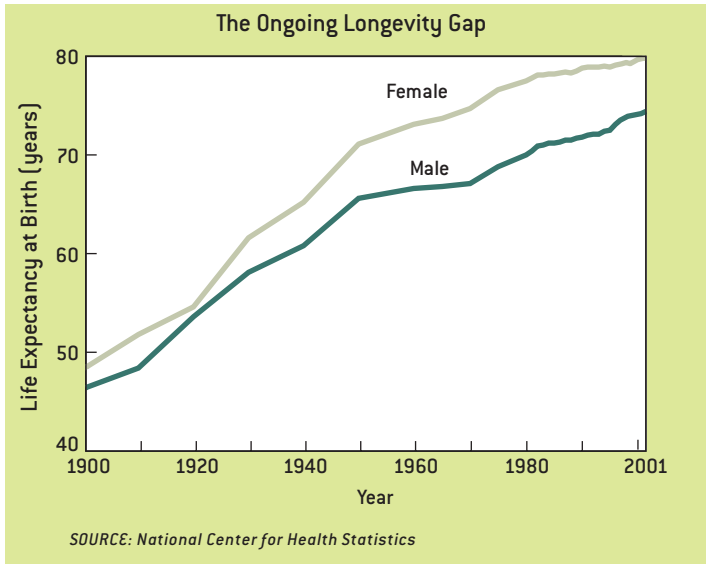
BEFORE 1960 smoking was far more prevalent among men than women. In 1955, for example, 56.9 percent of adult men were smokers, compared with only 28.4 percent of adult women. Since then, however, the smoking rates have converged: the prevalence among women peaked at 33.9 percent in 1965 and then slowly declined to 20.7 percent by 2001, but over the same period the rate among men plummeted to 25.2 percent, according to the Centers for Disease Control and Prevention.

If smoking is one of the causes of the longevity gap, why is the gap getting larger even as smoking rates have equalized? It is because smoking kills slowly. People who start smoking today will pay a steep price for their habit, but the payment won't come due for many years. Unfortunately, women are now suffering from a generation of tobacco abuse; as recently as 1960, lung cancer was rare in American women, but it is now their leading cancer killer, claiming 69,000 lives annually, according to the American Cancer Society.

Like smoking, alcoholism is traditionally a male problem that is increasingly shared by women. Small to modest amounts of alcohol protect a man's health, reducing his risk of heart disease. But larger amounts shorten life, increasing the incidence of hypertension, stroke, liver disease, accidents and various cancers. Heavy drinking has shortened the life spans of many American men.

Diet and Health Care

THE DIFFERING DIETS of men and women may also help explain why women live longer. In most cases, women have a healthier diet than men, eating a greater proportion of vegetables and a lower proportion of meat. A 1997 survey conducted by the U.S. Department of Agriculture found that men consume an average of 96 grams of fat a day, which accounts for approximately 44 percent of their daily caloric intake. Women, in contrast, get just 32 percent of their calories from fat. By 2000, men had dropped dietary fat to 33 percent, but in America, "real men" still don't eat broccoli. They should. The masculine ideal of meat and potatoes should give way to vegetables, fruits, grains and fish. Diet really does make a difference.



LIFE SPANS of American men and women have diverged for a century. The average life expectancy for women is 5.2 years greater than the life expectancy for men.

In 1992 Finnish scientists shocked the cardiological world when they published a report linking high levels of iron with a greatly increased risk of coronary artery disease. Because women lose iron with each menstrual period, the research fueled speculation that lower iron levels in the blood might partially account for the protection against heart attacks that is enjoyed by premenopausal women. A 1997 Finnish study seemed to corroborate the findings when it reported that men who donate blood have a lower risk of heart disease than men who do not donate.

Does iron explain the male vulnerability to heart disease? Probably not. Five American studies have examined the question, and each failed to corroborate an association between iron and heart disease. More studies will be needed to resolve the conflicting data; at present, although there are many good reasons for a man to donate blood, longevity does not appear to be one of them.

A more significant factor contributing to longevity is that women take care

THE AUTHOR

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LAURIE GRACE

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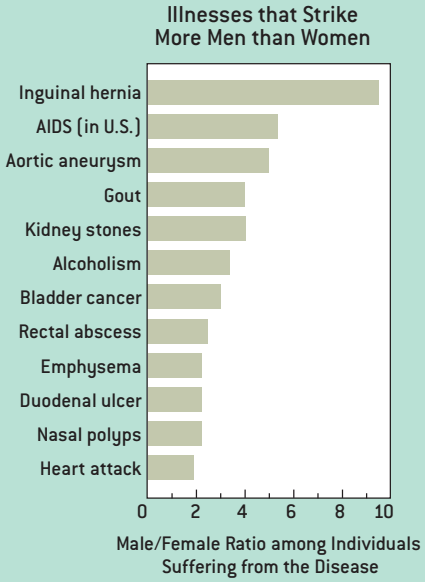
Male and Female Illnesses

Men and women each have medical problems that are unique to their sex; only men get prostate disease or testicular cancer, and only women face the risk of childbirth and diseases of the female reproductive organs. Although breast cancer is usually considered a female disease, men are not immune. In fact, about 1,400 American men are diagnosed with the disease every year—a small number compared with the 180,000 cases in American women but far from trivial.

Though not unique to either gender, other diseases have a marked predilection for men or women. For example, lupus and other autoimmune diseases that cause vascular inflammation are much more common in women than in men. The accompanying tables list the diseases that disproportionately strike males (*right*) and the 10 leading causes of death for American men and women (*below*). —*H.B.S.*



Leading Causes of Death in the U.S.

	Men	Women
1	Heart disease	Heart disease
2	Cancer	Cancer
3	Accidents	Stroke
4	Stroke	Chronic obstructive lung disease
5	Chronic obstructive lung disease	Diabetes
6	Diabetes	Alzheimer's disease
7	Pneumonia and influenza	Accidents
8	Suicide	Pneumonia and influenza
9	Kidney disease	Kidney disease
10	Liver disease	Blood infections

of their own health better than men do. Women are more diligent about checkups and preventive care. They are better at listening to their bodies and reporting discordant signals to their doctors. They even spend more time reading health publications. A walk down the health aisle of your local bookstore tells the tale: books on women's health greatly outnumber books on men's health, because publishers respond to consumer demand. It's true, too, of periodicals. Harvard Medical School launched its *Women's Health Watch* in 1993, but the *Harvard Men's Health Watch* did not make its debut until 1996.

If you look around a primary care physician's waiting room on an average day, you might think you were in a gynecologist's office. That is because women visit doctors much more often than men; a 1998 survey conducted by CNN and *Men's Health* magazine found that 76 percent of the female respondents had been tested for health problems in the past year, compared with only 64 percent of the men. The disparity is particularly pronounced between the ages of 15 and 44. Even when men do visit their doctors, they tend to minimize symptoms, gloss over concerns and even disregard medical advice. It is hard to know why men make such poor patients; busy work schedules and competing responsibilities and interests may play a role, but the macho mentality appears to be the chief culprit. Who can blame men for wanting to be John Wayne? But by following the example of that quintessential American he-man, men fail to take the simple steps that can protect them from heart disease and lung cancer—the very same illnesses that struck down Wayne at the age of 72.

Obesity and Stress

ANOTHER WAY that men can protect themselves from heart disease is through regular exercise. American men are slightly more likely to exercise than women, but about two thirds of men are not regularly active, and about one quarter do not participate in any physical activity at all. Largely because of lack of exercise and poor diet, an astounding two thirds of all American men are overweight (defined as having a body mass index of more than 25) or obese (an index greater than 30). A majority of American women are overweight, too, but there is a difference. Women tend to carry their weight on their hips and thighs (the "pear shape"), whereas men add it to their waistlines (the "apple shape"). Scientists do not know the reason for the difference, but it may have something to do with the fact that abdominal fat is more responsive

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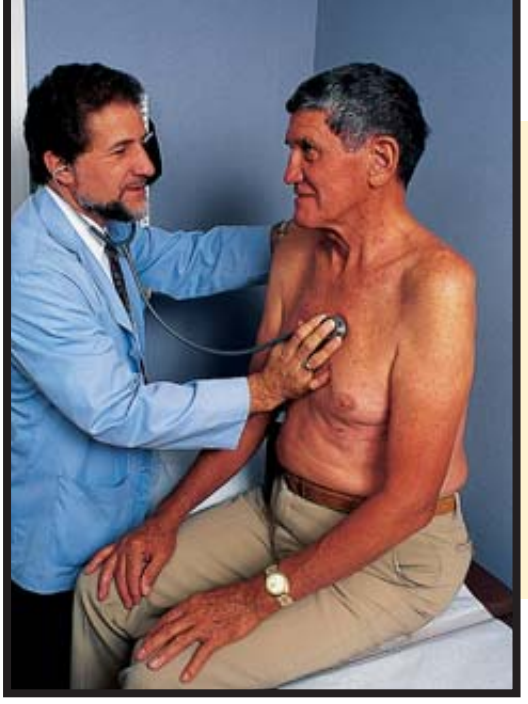

PHYSICAL CHECKUPS are anathema to many men. They visit doctors much less frequently than women do. And men often minimize their symptoms and disregard medical advice.

BACHMANN *Photo Researchers, Inc.*

How to Age Successfully

"Every man," wrote Jonathan Swift, "desires to live long, but no man would be old." Faced with the ever present tick of the clock, can a healthy middle-aged man tell if he is likely to remain free of the disabling diseases that often tarnish the golden years?

To find out, scientists evaluated 6,505 men between the ages of 45 and 68 who were in good health when the study began in the mid-1960s. As part of the famed Honolulu Heart Program, researchers tracked the men for nearly three decades. Of the men who survived to reach ages between 71 and 95, 40 percent remained free of both physical and cognitive impairment. The best predictors of successful aging were low blood pressure, low blood sugar, abstinence from tobacco and not being obese. It's a short and simple list—and it presents a set of goals that most middle-aged men can achieve with measures as simple as a proper diet and regular exercise. —*H.B.S.*

to adrenaline, the hormone produced in response to stress. When adrenaline is secreted into the bloodstream, fat cells in the abdomen tend to release larger amounts of free fatty acids. The resulting burst of energy was quite useful for prehistoric men in "fight or flight" situations—which may be why the apple shape evolved in men. But over time, free fatty acids can impair the normal functioning of the liver and increase the risk of diabetes, hypertension, heart attack and stroke. So abdominal obesity in men is much riskier than lower-body obesity in women. Aesthetics aside, most women are shaped better than men.

Stress itself may also be a factor that increases the chances of coronary disease. The stereotype of the hard-driving American male—succeeding at business but raising his blood pressure and clogging his coronary arteries in the process—contains more than a grain of truth. So-called Type A behavior—with its concomitant anxiety, stress and hostility—has been implicated as a heart disease risk factor, and this trait tends to be more prevalent in men than in women. Men who are feeling stress over their shorter life expectancy might be able to narrow the gap a bit by learning to relax.

Blame it on genes and hormones or on societal expectations, but men are typically more aggressive than women. Even in primitive societies, males assume the risk of hunting while women take on the safer task of gathering. In industrial societies, too, men pursue more dangerous occupations and hobbies. Violent encounters between men pose the greatest danger of all; even discounting wars, violence and trauma kill far more men than women. Men younger than 25 years are eight times more likely than women to fall victim to homicide. Women, it's true, face the unique challenge of childbirth, but maternal mortality is low in the modern world and does not begin to offset the male penchant for risk and violence.

What is more, men often fail to take advantage of social supports—the assistance provided by networks of friends and family members. The adage "people are good medicine" is true: support networks reduce the risks of many illnesses, ranging from the common cold to heart attacks. In some studies, at least, support groups even improve the outlook of cancer patients. In contrast, social isolation has been identified as a heart disease risk factor. Many studies have shown that women are more aware of their own feelings—and the feelings of other women—than men are. Women are not really from Venus, any more than men are from Mars, but good interpersonal communication may help explain why women on Earth live longer than men.

Furthermore, in most human societies, women nearly always assume the responsibility of child rearing. In some other species, though, males and females divide the chores more evenly. Could parental chores pay off in longevity? To find out, scientists at the California Institute of Technology examined the life expectancy of male and female monkeys, apes and humans. They found that in the species where males and females assume similar responsibilities for raising their young, the males and females have similar life expectancies. In the species where males do not participate in child rearing, however, the males do not live as long as the females. Of course, this does not necessarily mean that the act of parenting can add years to a man's life span; it is possible that the child-rearing males have greater longevity encoded in their genes because of natural selection. But young fathers might be wise not to dismiss it as monkey business when it's time to change a diaper or warm a bottle.

Why do women live longer than men? The explanation is complex, depending on both biological and behavioral differences between the sexes. In today's changing world, women seem to be acting more like men. When it comes to health, at least, it's a step in the wrong direction. With apologies to Professor Higgins, it's men who should be more like women. SA

MORE TO EXPLORE

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be post

AGING REMAINS inevitable, but scientists now have a strategy in place for figuring out how to retard the process.

Updated from the December 1999 issue

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will human aging be postponed?

IN THEORY, IT CERTAINLY CAN BE. YET NO SINGLE ELIXIR WILL DO THE TRICK. ANTIAGING THERAPIES OF THE FUTURE WILL UNDOUBTEDLY HAVE TO COUNTER MANY DESTRUCTIVE BIOCHEMICAL PROCESSES AT ONCE

BY MICHAEL R. ROSE

Cultures throughout history have aspired to postpone aging, thereby prolonging vitality and life itself. Today macrobiotic diets, recycled Hindu health practices, the latest fashions in gray-market hormone therapy and other forms of chicanery continue to fan the flames of hope. All these attempts to restore or sustain youthful vigor have just one thing in common: failure to achieve their goal.

Medical researchers have devised useful therapies for disorders that become more common with advancing age, such as cancer and heart disease. And over the past 120 years, sanitation systems and drugs that combat infectious disease have increased life expectancy in the developed nations by reducing premature death. But nothing delays or slows the innate processes that cause adults to age, to suffer a decline in physiological functioning as they grow older. Consequently, successful treatment of one illness late in life often means that another age-related problem soon takes its place. Infirmity remains the lot of those older than 80, however much the media may dote on the 90-year-old marathon runner.

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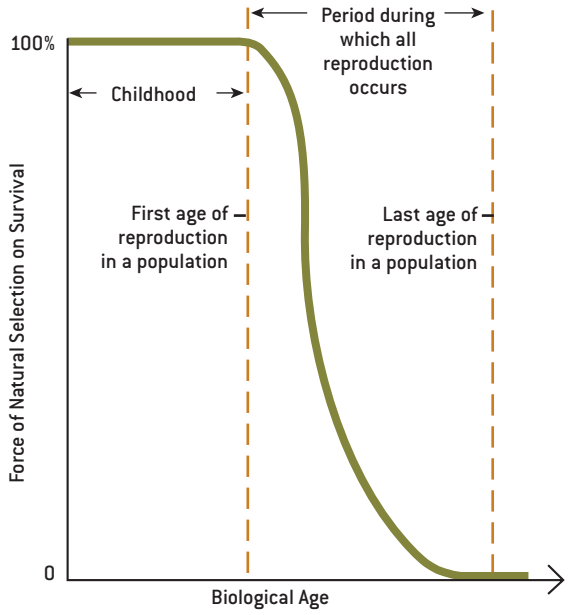
DISCOVERY BY evolutionary biologists explains why we age. Calculations show that the force of natural selection on survival in sexually reproducing populations drops soon after the earliest age of reproduction is reached. Aging has evolved because genes that produce deleterious effects late in life meet little or no opposition from natural selection and thus become rampant in the gene pool.



Instead senescence is the by-product of a pattern of natural selection that afflicts humans and other vertebrates but not vegetative sea anemones. More specifically, aging arises in sexually reproducing species because the force of natural selection declines after the start of adulthood.

This concept follows logically from general evolutionary theory. Heritable traits persist and become prevalent in a population—they are selected, in evolutionary terms—if those properties help their bearers to survive into reproductive age and produce offspring. The most useful traits result in the most offspring and hence in the greatest perpetuation of the genes controlling those properties. Meanwhile traits that diminish survival in youth become uncommon—are selected against—because their possessors often die before reproducing.

In contrast to deleterious genes that act early, those that sap vitality in later years would be expected to accumulate readily in a population, because parents with those genes will pass them to the next generation before their bad effects interfere with reproduction. (The later the genes lead to disability, the more they will spread, because the possessors will be able to reproduce longer.) Aging, then, creeps into populations because natural selection, which protects hardiness during youth, itself becomes increasingly feeble with adult age.

Two devastating genetic diseases dramatize this point. Progeria, caused by a chance mutation in one copy of the lamin A gene in a new embryo, leads to nightmarish deterioration during childhood. Many systems degenerate so quickly that the youngsters soon come to look as old as their grandparents. They commonly die of heart disease or stroke before their 15th birthday. Huntington's disease, which is also caused by a defect in one copy of a gene, manifests itself in middle age. In this case, the nervous system degenerates, eventually leading to death.

Progeria is rare, whereas Huntington's is relatively common among genetic disorders. Why? People with progeria die before reproducing. In this way, intense natural selection readily removes the progeria mutation from the gene pool whenever it arises. The mutation for Huntington's, on the other hand, does not interfere significantly with reproduction, because it does not yield disability until after people have produced all or most of

None of this means that postponing aging will be impossible forever. Since 1980 many studies have achieved that feat in animals, albeit by methods that cannot be applied to humans. The situation of aging research in 2004 is thus like that of atomic physics in 1929. Physicists by then had discovered previously unimagined quantum forces. The question was, Could they harness those forces? Aging research has made great progress recently, but has it advanced enough to defer our years of infirmity?

Not yet. To meet that goal, investigators need a much better understanding of the physiological processes that underlie senescence and influence life span. I am, however, optimistic that these processes can be discerned, because a more fundamental mystery has been solved: Why did aging evolve in the first place? The answer has enabled researchers to develop a rational strategy for unearthing the biochemical pathways that might be manipulated to extend our years of vigor.

What lies beyond the first significant postponement of aging later this century? Further postponement.

Natural Selection Snoozes

AGING DOES NOT OCCUR because of some universal defect in all cell types. If a singular, unavoidable flaw caused every cell to fail eventually, no animal would escape aging. But some do. For example, asexual sea anemones kept for decades in aquariums do not show failing health. Nor does aging derive from a genetic program designed by nature to block overpopulation.

JERRY GAY *Tony Stone Images (preceding pages)*; LAURIE GRACE

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MARK WEXLER *Woodfin Camp and Associates (left)*; PETER GINTER *Bilderberg Photo Archive (right)*

TWO GENETIC DISORDERS illustrate how weakened natural selection can allow deleterious late-acting genes to spread in a population. The person at the left had progeria, which causes rapid deterioration of the body during childhood; he looked old but was really a youngster. Progeria is rare because natural selection is strong in childhood and weeds out the causative gene; disease sufferers do not reproduce and so do not pass the gene to future generations. The man at the right had Huntington's disease, a neurodegenerative disorder that typically arises in middle age. Huntington's is more common because natural selection is powerless against it; by the time victims become symptomatic, they have usually bequeathed the destructive gene to half their offspring.

their children. It manifests at a stage when the force of natural selection is weak.

In the 1940s and 1950s J.B.S. Haldane and Nobelist Peter B. Medawar, both at University College London, were the first to introduce this evolutionary explanation of aging. W. D. Hamilton of Imperial College London and Brian Charlesworth of the University of Sussex then made the thesis mathematically rigorous in the 1960s and 1970s.

In their most important result, Hamilton and Charlesworth established that for organisms that do not reproduce by splitting in two, the force of natural selection on survival falls with adult age and then disappears entirely late in life. Because natural selection is the source of all adaptation, and thus of health, the hardiness of older organisms declines as natural selection fades out. Eventually, with the continued absence of natural selection at later ages, survival may be so imperiled that optimal conditions and medical care may be unable to keep the older individual alive.

Since the 1970s the original mathematical proofs have been confirmed experimentally many times, most often by manipulations that deliberately prolong the period of intense natural selection in laboratory animals. Investigators extend this period by delaying the age at which reproduction begins; they discard all fertilized eggs produced by young animals and use only those produced late in life. As a result, only individuals who are robust enough to reproduce at an advanced age will pass their genes to the next generation.

If the declining strength of natural selection after the start of reproduction really does explain the evolution of aging, then progressively retarding this drop for a number of generations in a test population should lead to the evolution of significantly postponed aging in that lineage. This prediction has been shown to be true in fruit flies of the genus *Drosophila* that have had reproduction delayed across 10 or more generations. As a result of these experiments, scientists now have stocks that live two to three times as long as normal ones and remain healthy longer as well.

The flies that display postponed aging are surprisingly perky. They do not merely sustain normal biological functions for longer periods; they display superior capabilities at all adult ages. In youth and later, they are better able to resist such typically lethal stresses as acute desiccation and starvation. They also show more physical prowess than their like-aged counterparts do, being able to walk and fly for longer periods.

If people could be treated in the same way as fruit flies, the problem of postponing human aging could be solved by forcibly delaying childbirth over many generations. Such practices would be barbaric, however, as well as extremely slow in producing results. Those who wish to delay aging must therefore find other methods, ones that would essentially mimic the physiological changes brought about by generations of postponed breeding. (A note to those who are tempted to try postponing breeding: the practice will not yield any immediate benefit to

THE AUTHOR

MICHAEL R. ROSE is professor of evolutionary biology at the University of California, Irvine. He concentrates on experimental tests, mainly in fruit flies, of evolutionary theories of aging, fitness and life histories. Rose says it has been at least 10 years since he has been openly ridiculed for explaining aging in terms of evolution.

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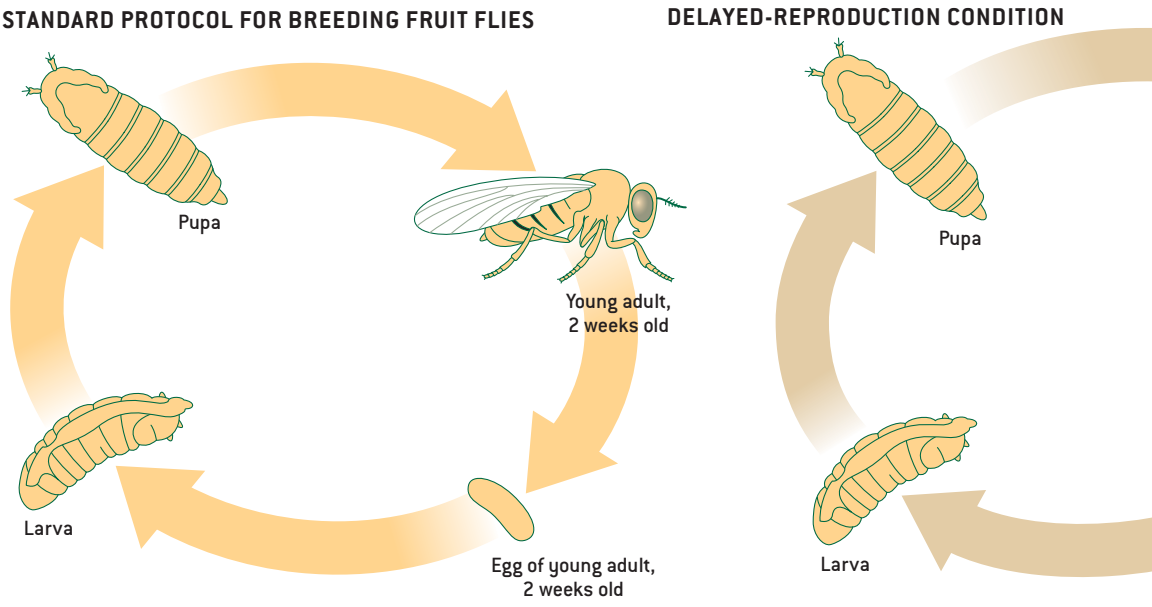


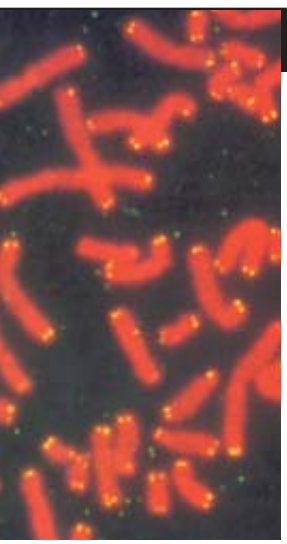
FRUIT FLY experiments support the notion that aging is caused by the declining power of natural selection during adulthood. Scientists allowed a control group (*left*) to reproduce soon after reaching maturity, thereby keeping the period of intense natural selection short. They delayed reproduction in another group (*right*), thereby prolonging the period of intense natural selection. After many generations, such manipulation delayed aging in both males and females in the second group and led to greater longevity (*graphs*).

you or your future children. It would probably take about 10 generations to increase longevity at all and centuries to yield a significant increase in life span.)

Clues to Biochemical Causes

EVOLUTIONARY THEORY and some crude experiments suggest that hundreds of genetically determined biochemical pathways—cascades of molecular interactions—influence longevity and might thus be manipulated to postpone aging. So far, however, only a handful of genes that could be involved have been discovered, principally in the nematode worm *Caenorhabditis elegans* and in the fruit fly *Drosophila melanogaster*. Whether results in these organisms apply to humans remains to be determined.

A few studies have been done in people as well. For instance, genetic analyses of French centenarians have identified two variable genes that might participate in postponing aging in people: one codes for apolipoprotein E (a protein involved in cholesterol transport), the other for angiotensin-converting enzyme (involved in blood pressure regulation). In each case, particular alleles, or variants, of the genes have been found to be more common in the centenarians than in younger adults.



TELOMERES that cap chromosomes (*highlighted by fluorescence*) regulate cell longevity.

ROBERT K. MOYZIS

NO EASY FIXES

HOMO SAPIENS are already relatively long-lived, at least for organisms that are not trees. But many of us would like to live even longer, especially if we can do so in good health. That desire, however, may sometimes blind us to the reality that any promises of easy fixes are sure to be empty.

Among the potential therapies that have been publicized in recent years are exercise, diet restriction, and delivery of such substances as growth hormone, the enzyme telomerase and antioxidants. Exercise improves functioning for as long as it is pursued diligently, but it has not been shown to increase long-term survival; in addition, its beneficial physiological effects do not persist very long after a person returns to a more sedentary way of life. Diet restriction works in rodents but has not been studied systematically in humans and is not practical for most people. And arbitrarily cranking up the levels of any hormone in the body is potentially dangerous.

Many news reports have focused on the ability of telomerase to delay senescence of human cells in the test tube. This enzyme acts on structures called telomeres, which cap the ends of chromosomes. Telomeres shrink a bit every time a human cell divides; when the length drops below a set threshold, cells stop dividing. Some investigators have suggested that drug therapies that preserve telomeres might enable dividing cells to reproduce and remain healthy indefinitely; they also have proposed that such preservation might retard aging in whole organisms. They have not, however, managed to prove their case by holding off the aging of any living creature. Further, anything that contributes to the immortality of cells runs the risk of promoting cancer.

Research in fruit flies and other organisms does seem to implicate free radicals—highly destructive, oxidizing molecules made routinely by the body itself—in aging. Indeed, in fruit flies, a gene variant giving rise to an unusually active form of superoxide dismutase, a scavenger that neutralizes destructive free radicals, is associated with robust longevity. If oxidation reactions are involved in human aging, then blocking the production of free radicals or scavenging them might help delay senescence. Despite claims to the contrary, though, scientists do not yet know how to achieve those effects safely in people, and no studies have determined whether such interventions would, in fact, be successful. —*M.R.R.*

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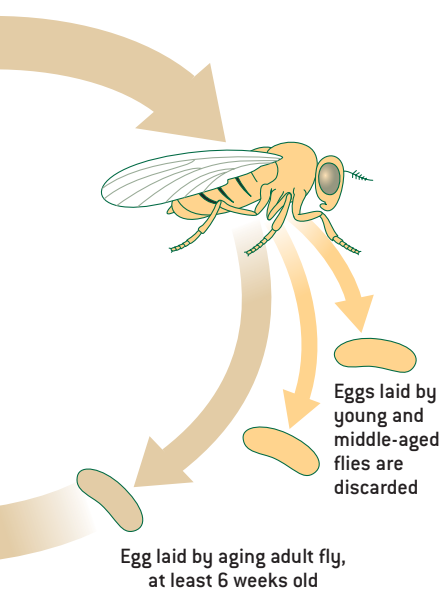

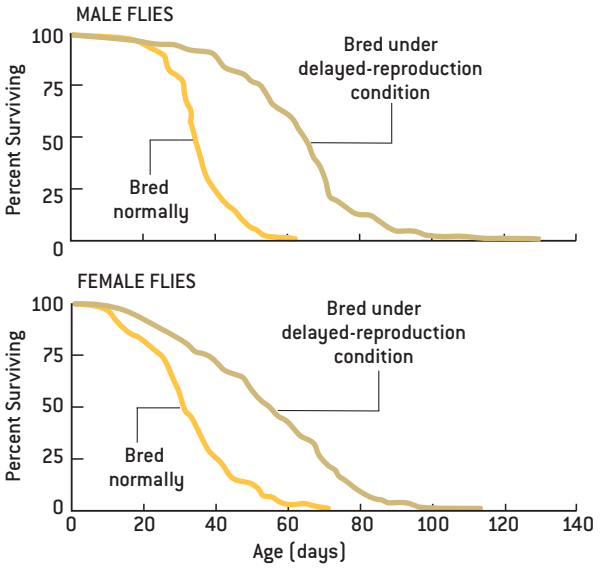

The French results do not point to any antiaging therapies, however. No one knows exactly how the alleles common in long-lived people might combat aging. Moreover, even if those alleles, or ones first uncovered in worms and fruit flies, were linked to extended health in people, the discovery would still constitute only one step toward delaying senescence. Alteration of the multifactorial aging process is likely to require manipulation of several, perhaps many, biochemical pathways.

A useful way to find alleles that might affect aging would be to compare the genetic makeup of normal animals and of those displaying deferred aging. Fortunately, the same approach that tested the evolutionary theory of aging can be applied to reveal large suites of genes with an influence on life span. Fruit flies that have had their longevity extended by delayed reproduction turn out to have a different mix of alleles than occurs in run-of-the-mill fruit flies. These alleles were not selected in advance and delivered to the long-lived flies. Rather, in response to delayed reproduction, natural selection constructed organisms that exhibited postponed aging.

Identifying the specific alleles that differ in long-lived and normal animals will help those of us who study aging to develop treatments that emulate or enhance the effects of beneficial alleles and that counter the effects of deleterious ones. Candidate therapies will, of course, have to be tested successfully in laboratory animals before being evaluated in people.

Technology Will Set the Pace

WHETHER FRUIT FLIES, rodents or other animals are the subjects of comparative studies, the work will not be easy. Scientists will not only have to identify hundreds or thousands of alleles that occur most frequently in long-lived subjects, they will also have to decipher the biological functions and unique features of the corresponding proteins. The collected technologies needed to perform these tasks fall under the rubric of "functional genomics," which is very much a work in progress. Only if that progress is rapid enough will we see human aging postponed significantly by 2050.

This statement may seem puzzling in light of never-ending publicity about the potential antiaging effects of any number of interventions. Yet, as I said earlier, no proposed therapy has yet been proved to work, and none is likely to have a dramatic impact on its own [*see box on opposite page*].

What lies beyond the first significant postponement of human aging, sometime later in this century? Further postponement. Delaying human aging is not an all-or-none objective, like putting a person on the moon. Our survival and function in later life will be improved cumulatively, much as cars have been improved progressively over the past century of manufacturing. I see no limit to how long human life can be extended if scientists learn how to turn on antiaging genes in the young or how to prepare cocktails of drugs that serve the same purpose as genetic engineering. Yet no one knows even the basic features that successful interventions will need to have.

The postponement of human aging raises difficult issues for public policy and personal ethics. How will Social Security fare in a postponed-aging future? What will happen to retirement at 65? What of our children's expectation that we will die and leave them an inheritance? Will there be even more overpopulation? Isn't there something immoral about the elderly clinging to life? These difficult questions concern many thoughtful people.

Still a conjectural achievement, the postponement of human aging poses no direct threat or incentive to anyone in 2004. But in 2050 it may be a reality that gives headaches to Congress and high spirits to the middle-aged. SA

MORE TO EXPLORE

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CHRISTOPH BLUMRICH (*illustration*); LAURIE GRACE (*graphs*)

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THERE MAY BE A WAY TO PREVENT OURSELVES FROM RUSTING FROM THE INSIDE OUT

a radical proposal

BY KATHRYN BROWN

EVERETT COLLECTION

WIZARD OF O_2: Water killed the Wicked Witch in Oz, but oxygen may kill us, oxidizing our cells the way it rusted Dorothy's pal the Tin Man.

You can drop cigarettes. Avoid alcohol. But there's one toxin you just can't dodge: oxygen. With every gulp of air, oxygen gives you life. Some of it, however, gets converted inside your cells into a radical molecule that can wreak havoc, degrading those same cells and others. A growing number of experts say this damage causes aging. They also think they may one day be able to fend off oxygen's ill effects and help us live a lot longer.

Scientists have long known that oxygen is capricious. As molecules go, it gets around, reacting with all kinds of things. Mostly, that's good. Oxygen combines with fats and carbohydrates, in a part of cells known as the mitochondrion, to churn out the energy that gets you through the day. But the conversion isn't perfect. A small amount of oxygen is regenerated in a nasty form called a free radical, or oxidant—the very critter that causes metal to rust. The oxidants careen about, binding to and disrupting the membranes, proteins, DNA and other cell structures that make your body work. Over time, this damage adds up, and the result just might be an older, frailer you.

According to one estimate, oxidants bombard the DNA inside every one of our cells roughly 10,000 times a day. Thankfully, most of the assailants are intercepted by a small army of antioxidant chemicals. Proteins also patch up the damage caused by the radicals that do get through. As scientists say, the house is always getting dirty, and we're always trying to clean it up. But eventually, the theory goes, our tired cells get less efficient at repelling free radicals and mopping up oxidative messes, and the damage accumulates. We begin to rust from the inside out.

If oxidants do send us crumbling into old age, then ramping up our biochemical defenses should extend life. That's what scientists are finding, at least in the flies, rats, worms and other animals they have under scrutiny in the laboratory. Whether the techniques they are pursuing will ever lengthen life in humans remains an open question. But some researchers think they're getting close to an answer. "The key is to really understand how oxidative damage works, and we're learning that," says biochemist Bruce N. Ames of the University of California at Berkeley. "I'm convinced life expectancy will get longer a lot faster than anybody thinks."

The Original Pollutant

OXYGEN'S CHECKERED PAST goes way back—about two billion years. Around that time, scientists believe, cyanobacteria began releasing more and more oxygen into the earth's atmosphere, until many organisms were forced to either accommodate the gas or risk being degraded by its corrosive nature. Over time, some particularly oxygen-adept bacteria evolved into mitochondria, the tiny powerhouses in all human cells that use oxygen to help turn food into energy.

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The "free radical theory of aging" was first laid out almost half a century ago by Denham Harman of the University of Nebraska. The idea won credibility in 1969, when scientists identified a key antioxidant, superoxide dismutase (SOD), an enzyme that breaks down the harmful superoxide, a leader among the various free radicals that can form inside the human body. Soon researchers began to realize that mitochondria created oxidants in high amounts. And by now dozens of experiments have linked oxidative damage and aging.

Until recently, however, that link had been a matter of indirect correlation. In the lab, for instance, some young human cells do far better than older cells at resisting or repairing oxidative damage, whether the cells are being doused with hydrogen peroxide or stuck inside a chamber filled with pure oxygen. Also, lab flies, worms and mice carrying genetic mutations that proffer long life tend to withstand oxidative assaults better than their peers. "All these studies suggest oxidative damage may be an important part of aging, but they lack the kind of direct experiments to nail that link down," notes John Tower, a molecular biologist at the University of Southern California. "The question is, If we actually alter oxidative stress, will it extend life?"

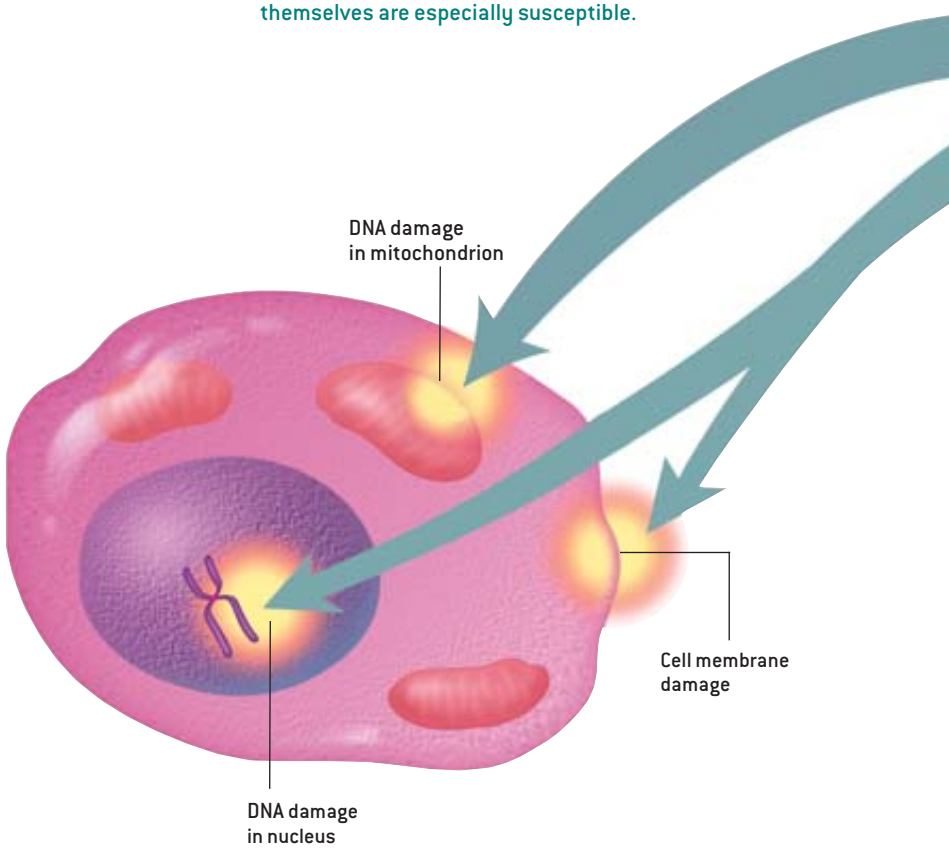
To find out, Tower and his U.S.C. colleague Jingtao Sun reared fruit flies with an engineered protein that could—when exposed to heat—turn up the activity of SOD and another antioxidant, catalase. The flies started life in the lab normally, along with a control group of flies. Then, on the fifth day, the experimental flies got pulses of heat, ratcheting up their antioxidant defenses. The results were striking. Most of the everyday flies keeled over long before six weeks—but those with supercharged SOD, in particular, survived an average of 48 percent longer. "That's pretty convincing evidence that overexpression of SOD extends life," Tower says.

That's not the only evidence. Nearly 10 years ago William Orr and Rajindar Sohal of Southern Methodist University in Dallas equipped their own flies

CELLULAR DAMAGE AND DEFENSE

In cell metabolism, the mitochondria convert glucose and oxygen into energy. Oxygen radicals also form as a normal by-product.

The highly reactive oxygen radical can bind with other molecules, damaging cell proteins and membranes. The DNA molecules in the mitochondria themselves are especially susceptible.



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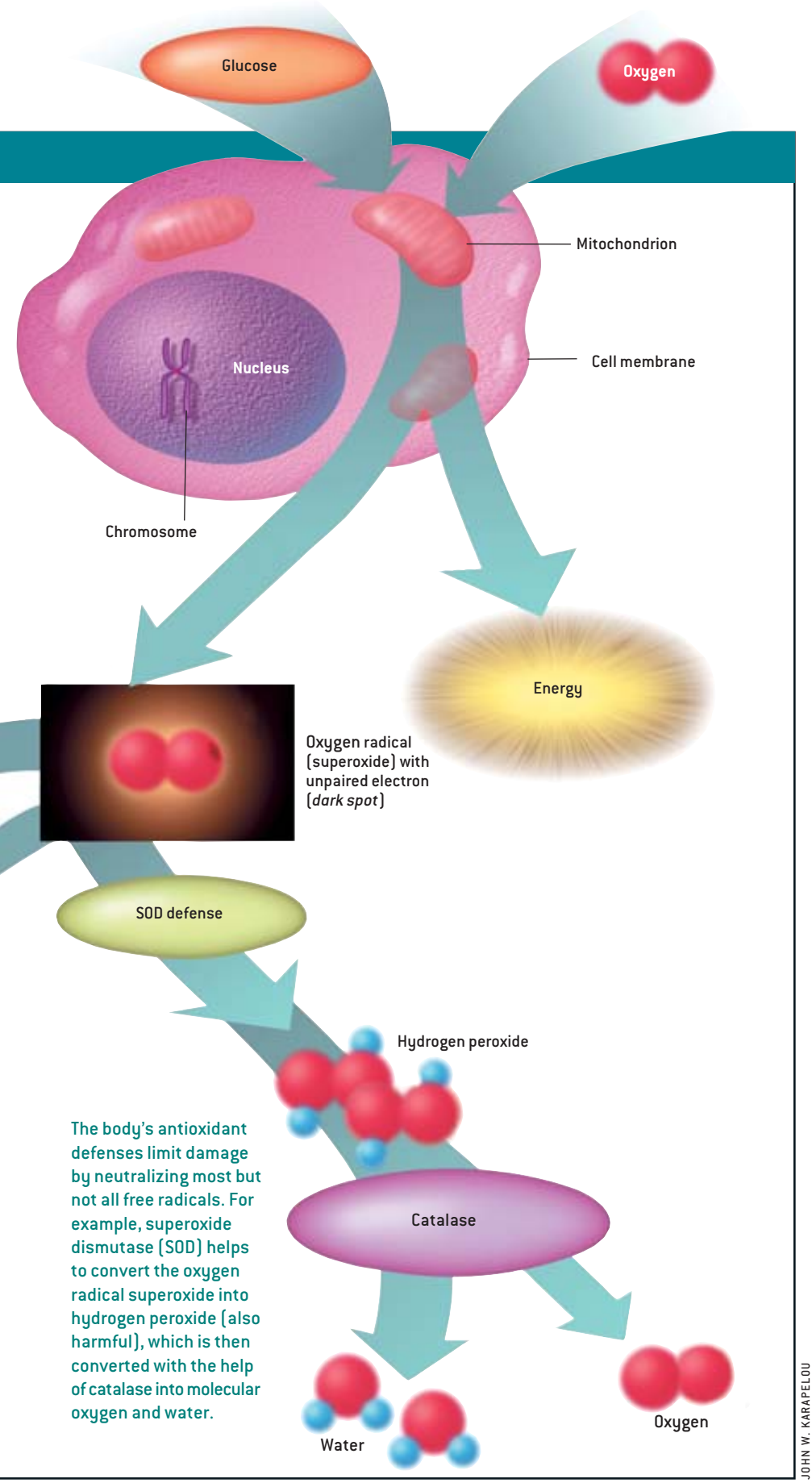

The body's antioxidant defenses limit damage by neutralizing most but not all free radicals. For example, superoxide dismutase (SOD) helps to convert the oxygen radical superoxide into hydrogen peroxide (also harmful), which is then converted with the help of catalase into molecular oxygen and water.

JOHN W. KARAPELOU

with extra copies of genes for SOD and catalase. Those flies lingered up to a third longer than their normal maximum life span—and seemed to age more slowly along the way, exhibiting higher energy, faster movements and less oxidative damage. There is a caveat, however, highlighted in a recent follow-up study by Sohal and his colleagues. The team has found that genetic background—the luck of inheritance—significantly affects longevity. Organisms already blessed with genes that confer a longer than average life span stand to gain less from a dose of overexpressed SOD than "at risk" organisms genetically slated to die earlier. SOD may just level the playing field a bit. So far, Orr adds, researchers have been unable to extend life by manipulating SOD expression in mouse models.

Intercepting the Interloper

IN THE MEANTIME, scientists hope to pinpoint exactly where oxidants do their dirtiest work—and ways to intervene. The idea, says molecular biologist John P. Phillips of the University of Guelph in Ontario, is to tailor therapies to the most important injured cells, rather than trying to fight oxidative damage throughout the body. Phillips has one candidate cell in mind: the motor neuron, which directs muscles from the brain and spinal cord. People with a paralyzing disease called familial amyotrophic lateral sclerosis die early, with heavily damaged motor neurons as well as mutations in SOD. Maybe motor neurons are a critical target of oxidants, kick-starting or dominating the process of aging.

To test that idea, Phillips and his coworkers bred fruit flies with a jolt of one of the human superoxide dismutase compounds, SOD1, to be expressed only in the flies' motor neurons. Sure enough, the bugs lived 40 percent longer than normal. And those extra days were lively ones. "We didn't just delay dying, so that we had geriatric flies living longer," Phillips says. "The extended time of life was youth." In contrast, boosting SOD1 levels in unrelated muscle cells seems to have had no effect on the flies' life span, he adds. Still, ques-

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tions remain. "We don't really know why these animals are living longer," Phillips concedes. To pin down SOD's relevance, the team has been spiking different types of neurons with the antioxidant to see how the various cells react.

Another target for protection is the mitochondria inside all cells. Because these tiny powerhouses are the very source of harmful oxidants, they're the first cell structures to be clobbered by the chemicals. In a 1998 study Sohal and his co-worker Liang-Jun Yan exposed flies to high doses of pure oxygen and then went looking for signs of oxidants operating in the flies' mitochondrial membranes. Rather than far-flung havoc, they found that oxidants targeted several vulnerable proteins, attaching to their strings of DNA, forcing them out of work and upsetting the entire cell's ability to act normally. "Free radical damage during aging is not random, causing decline all around our cells," Sohal says. "We're talking about damage that's very selective, and that may mean aging comes from specific biochemical losses."

Proof of this notion would be good news, Ames says. "The key thing is to understand how aging really works. If it's the decay of mitochondrial DNA, well, we can do things to beef up these old mitochondria."

Ames, Tory Hagen of Oregon State University and their colleagues have done just that. For several weeks in 1999, they fed a group of older rats food laced with lipoic acid (which converts to a potent antioxidant) and acetyl carnitine—chemicals used only by the mitochondria. The rats' liver cells deflected oxidant intruders with greater resiliency. What's more, the senior rats scrambled around with new spirit, a sleeker look, and better functioning brains and immune systems. "I don't want to say we've gone so far as turning old rats back into young rats," Ames says, "but that sure looks like what's going on in the mitochondria."

Supermarket Solutions

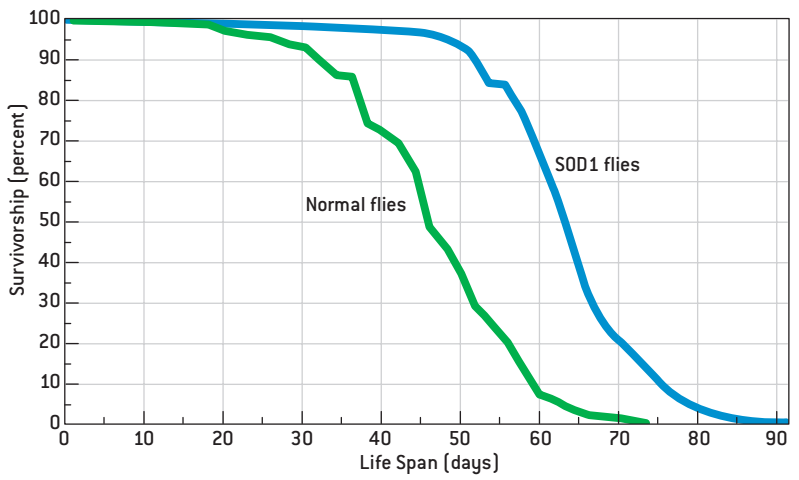
IF ANTIOXIDANTS WORK for flies and rats, what about us? Can you down a daily supplement that will extend your years? Don't count on it. "Everybody is talking about popping antioxidant vitamins," Phillips groans. "The evidence is strong that taking moderate amounts of vitamin C and E is not harmful, but the evidence that it's actually useful for delaying aging is very thin." For one thing, researchers say, your body can absorb only so much of these vitamins; the rest goes the way of other wastes. Also, in the industrial world, most of us get enough of the basic antioxidants in our daily diets. In contrast, lab animals that live unusually long with extra antioxidants may be deficient in those chemicals to begin with.

Even if antioxidant supplements do boost your defenses against free radicals, it's tricky to know which ones—or how much—to take. As with any ingredient, too much can be a bad thing. In 1996, for instance, two large studies made news when researchers discovered that beta-carotene supplements—thought to help ward off some types of cancer—actually increased rates of lung cancer among smokers who were taking the pills. Some antioxidants hawked in health food stores will never do any good; walk right past those bottles of SOD, catalase and glutathione peroxidase, because these compounds must be created inside the body. When swallowed, they are simply broken down in digestion and rendered useless, researchers state.

Still, there are a few antioxidants that hold promise, Ames says, such as lipoic acid, which directly protects the mitochondria. Perhaps, he adds, some of the more obscure antioxidants decrease in the body as we age, leaving us more vulnerable to oxidative damage. If that's the case, absorbing extra amounts of these conditional nutrients might slow aging's cellular effects. "We just don't know yet," Ames says.

Indeed, there are many unknowns. What proportion of aging changes in cells are the result of oxidative damage? Is there a way to reduce the rate of oxidants the body churns out, rather than simply boosting antioxidants? And what do all these long-lived lab mutants really explain about oxidative stress in people? Sohal worries that some of the most touted studies are misleading. For instance, biologists have won lots of attention by reporting that in worms, single mutations in a gene called *daf-2* can double life span, partly by resisting ox-

RUST INHIBITION: AN ENZYME EXTENDS LIFE



LONGER YOUTH: Fruit flies bred with a dose of SOD1, an antioxidant enzyme that breaks down free radicals, lived 40 percent longer than normal fruit flies did in a University of Guelph laboratory. Notably, the phase of life extended was youth, not old age.

LAURIE GRACE; SOURCE: JOHN P. PHILLIPS *University of Guelph*

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idative stress. But this is a "bogus kind of life extension," charges Sohal, because the worms' metabolism (energy level) plummets during their extra time on earth. "It's just like going to sleep for three years and calling that three extra years of life," he says. The extra time is akin to hibernation, Sohal adds, so any therapy based on it would rob people of the energy they normally have.

The most basic challenge is understanding aging itself. Growing old is a slow, subtle process that's hard to define with blood tests or cellular studies. Oxidants can muddy the picture. After all, these omnipresent molecules can strike a cell's proteins, fats or DNA, all very different beasts.

In the short run, researchers may first unravel the role of oxidants in specific diseases of aging, such as Alzheimer's and Parkinson's. People who suffer from these conditions show telltale signs of oxidative damage in the brain. Eventually these studies may inch scientists closer to understanding basic brain changes during aging. There may be reason for optimism. Some 10 years ago University of Kentucky researchers were first to report that high levels of a synthetic antioxidant, PBN, can decrease harmful oxidative proteins in the brains of old gerbils. Could aging be a treatable process?

Self-Imposed Treatment

SOME INDIVIDUALS are prescribing their own treatments. According to one idea, you can starve yourself, cutting back on calories until your metabolism drops so low that fewer free radicals are formed in the first place. A more pleasant alternative, perhaps, is munching on fruits and vegetables that are high in antioxidants. In 1999 neuroscientist James A. Joseph of Tufts University and his colleagues reported that senescent rats fed extracts of spinach, blueberries or strawberries for eight weeks showed marked declines in oxidative stress in their brain cells, as well as improved memory and coordination. The most successful rats noshed on blueberries—the equivalent of a cup a day for humans.

The research also highlights how much scientists have to learn about the processes that contribute to aging. Apparently, it's the blend of ingredients inside blueberries—not just isolated antioxidants—that benefited the racy rats. Studying the rats' brain cells, Joseph was surprised to find relatively few signs of increased antioxidants. Instead he found a host of cell changes, from better anti-inflammatory activity to more pliable membranes—all of which could act together to combat aging changes. More recently, Joseph's lab has highlighted the role of flavonoids, compounds inside blueberries that may actually help generate new cell growth in brain areas mediating memory and also help increase neuronal signaling.

"If you take a supplement, you never get the benefit of a fruit or vegetable that contains hundreds of compounds," Joseph says. Right now researchers can't even identify all the compounds, much less explain how they might work together to fight free radicals. The answers could be years in coming. In the meantime, he asks, why not stroll down the produce aisle? A few berries might just offset a little oxidation—or at least make the wait for answers to aging that much sweeter. SA

Kathryn Brown is a science writer in Alexandria, Va.

THE ANTIOXIDANT DIET

YOUR BEST BET for fending off cellular damage from free radicals, scientists say, is to maintain a healthy supply of antioxidant compounds by eating fruits and vegetables—not by taking a pill. Here are some foods rich in antioxidants.

Fruits: blueberries, cherries, kiwis, pink grapefruit, oranges, plums, prunes, raisins, raspberries, red grapes, strawberries

Vegetables: alfalfa sprouts, beets, broccoli flowers, Brussels sprouts, corn, eggplant, kale, onions, red bell peppers, spinach

KEVIN R. MORRIS *Corbis*; SOURCE: U.S. AGRICULTURAL RESEARCH SERVICE

MORE TO EXPLORE

Feeding Acetyl-L-Carnitine and Lipoic Acid to Old Rats Significantly Improves Metabolic Function while Decreasing Oxidative Stress. Tory M. Hagen et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 9, No. 4, pages 1870–1875; February 19, 2002.

Induced Overexpression of Mitochondrial Mn-Superoxide Dismutase Extends the Life Span of Adult *Drosophila melanogaster.* J. Sun et al. in *Genetics,* Vol. 161, No. 2, pages 661–672; June 2002.

Mechanisms of Aging: An Appraisal of the Oxidative Stress Hypothesis. Rajindar S. Sohal et al. in *Free Radical Biology and Medicine,* Vol. 33, No. 5, pages 575–586; September 2002.

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The Serious Search for an Antiaging Pill

In government laboratories and elsewhere, scientists are seeking a drug able to prolong life and youthful vigor. Studies of caloric restriction are showing the way

By Mark A. Lane, Donald K. Ingram and George S. Roth

No treatment on the market has been proved to slow human aging—the buildup of molecular and cellular damage that increases vulnerability to infirmity as we grow older. But one intervention, consumption of a low-calorie yet nutritionally balanced diet, works incredibly well in a broad range of animals, increasing longevity and prolonging good health. Those findings suggest that caloric restriction could delay aging in humans, too.

Unfortunately, for maximum benefit, people would probably have to reduce their caloric intake by roughly 30 percent, equivalent to dropping from 2,500 calories a day to 1,750. Few mortals could stick to that harsh a regimen, especially for years on end. But what if someone could create a pill that mimicked the physiological effects of eating less without actually forcing people to go hungry? Could such a caloric-restriction mimetic, as we call it, enable people to stay healthy longer, postponing age-related disorders (such as diabetes, atherosclerosis, heart disease and cancer) until very late in life?

We first posed this question in the mid-1990s, after we came upon a chemical agent that, in rodents, seemed to reproduce many of caloric restriction's benefits. Since then, we and others have been searching for a compound that would safely achieve the same feat in people. We have not succeeded yet, but our failures have been informative and have fanned hope that caloric-restriction, or CR, mimetics can indeed be developed eventually.

Our hunt for CR mimetics grew out of our desire to better understand caloric restriction's many effects on the body. Scientists first recognized the value of the practice more than 60 years ago, when they found that rats fed a low-calorie diet lived longer on average than free-feeding rats and had a reduced incidence of conditions that become increasingly common in old age. What is more, some of the treated animals survived longer than the oldest-living animals in the control group, which means that the maximum life span (the oldest attainable age), not merely the average life span, increased. Various interventions, such as infection-fighting drugs, can increase a population's average survival time, but only approaches that slow the body's rate of aging will increase the maximum life span that an animal can achieve.

The rat findings have been replicated many times and extended to creatures ranging from yeast to fruit flies, worms, fish, spiders, mice and hamsters. Until fairly recently, the studies were limited to short-lived creatures genetically distant from humans. But long-term projects under way in two species more closely related to humans—rhesus and squirrel monkeys—sug-

CALORIC-RESTRICTION MIMETIC would, if successful, enable humans to derive many of the health and life-extending benefits seen in animals on restricted diets—without requiring people to go hungry.

STUART BRADFORD

Updated from the August 2002 issue

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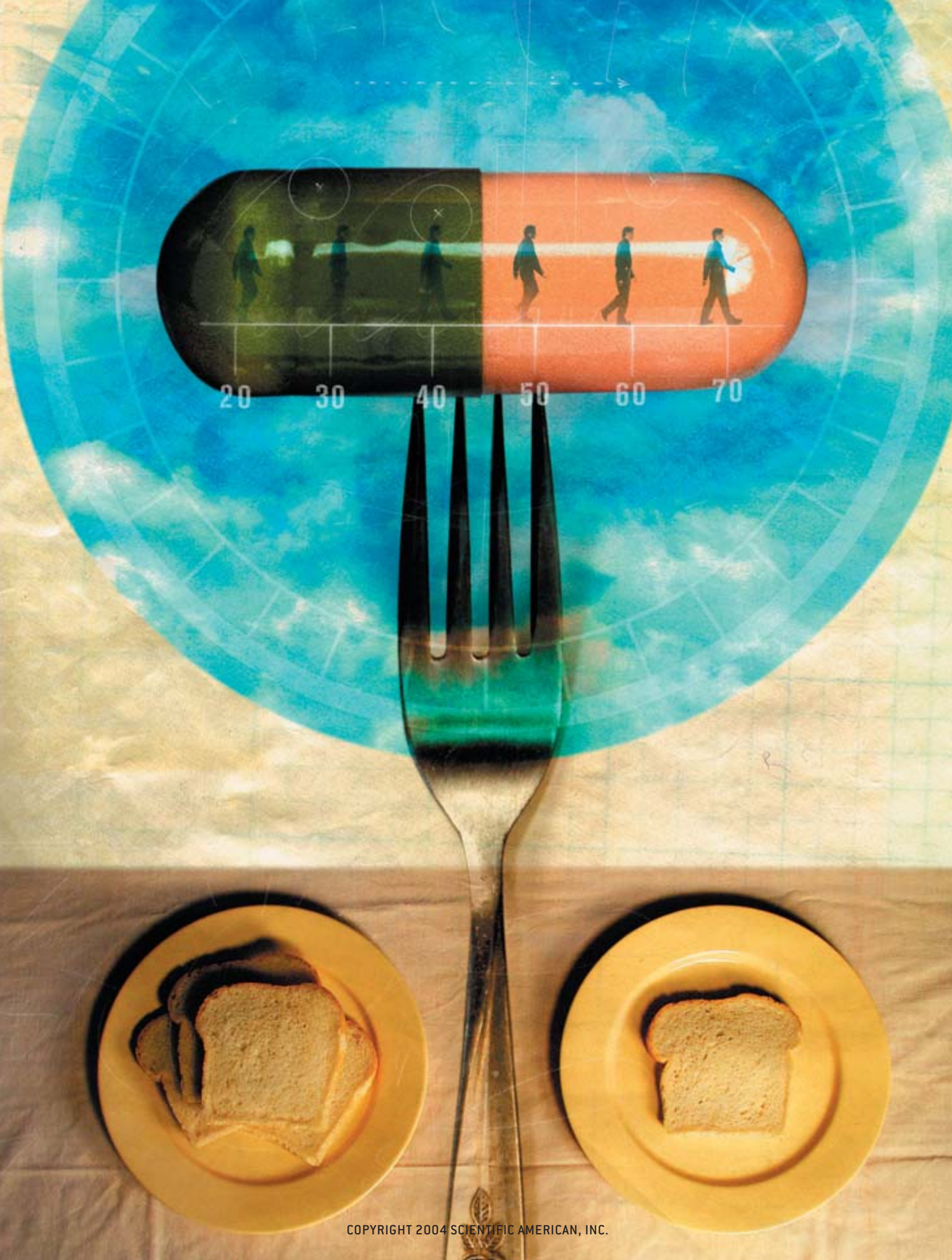

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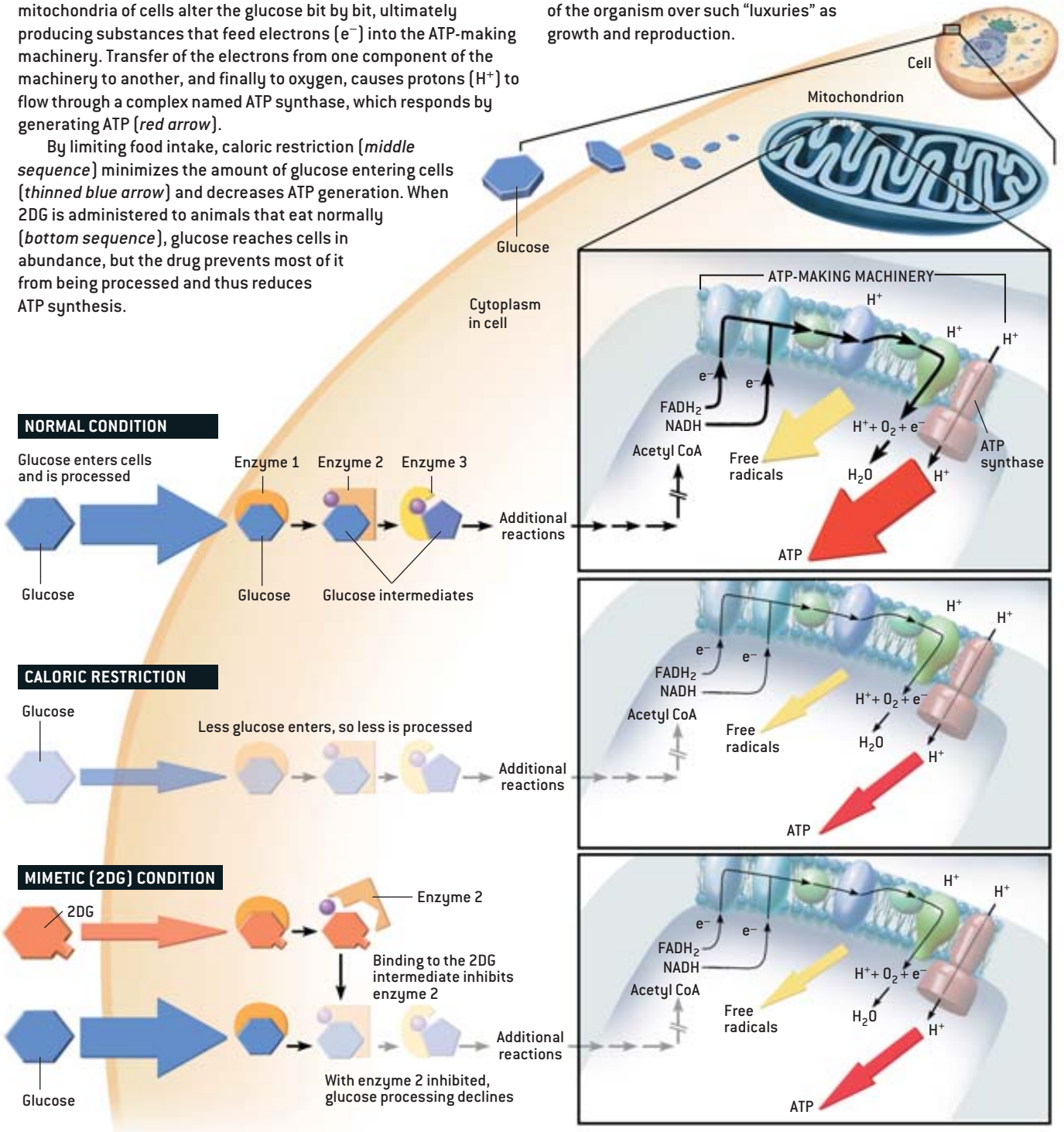
HOW A PROTOTYPE CALORIC-RESTRICTION MIMETIC WORKS

THE BEST-STUDIED CANDIDATE for a caloric-restriction mimetic, 2DG (2-deoxy-D-glucose), works by interfering with the way cells process the sugar glucose. It has proved toxic at some doses in animals and so cannot be used in humans. But it has demonstrated that chemicals can replicate the effects of caloric restriction; the trick is finding the right one.

Cells use the glucose from food to generate ATP (adenosine triphosphate), the molecule that powers many activities in the body (*top sequence*). More specifically, after glucose enters cells (*blue arrow*), a series of enzymatic reactions in the cytoplasm and mitochondria of cells alter the glucose bit by bit, ultimately producing substances that feed electrons (e^-) into the ATP-making machinery. Transfer of the electrons from one component of the machinery to another, and finally to oxygen, causes protons (H^+) to flow through a complex named ATP synthase, which responds by generating ATP (*red arrow*).

By limiting food intake, caloric restriction (*middle sequence*) minimizes the amount of glucose entering cells (*thinned blue arrow*) and decreases ATP generation. When 2DG is administered to animals that eat normally (*bottom sequence*), glucose reaches cells in abundance, but the drug prevents most of it from being processed and thus reduces ATP synthesis.

Researchers have proposed several explanations for why interruption of glucose processing and ATP production might retard aging. One possibility relates to the ATP-making machinery's emission of free radicals (*yellow arrows*), which are thought to contribute to aging and to such age-related diseases as cancer by damaging cells. Reduced operation of the machinery should limit their production and thereby constrain the damage. Another hypothesis suggests that decreased processing of glucose could indicate to cells that food is scarce (even if it isn't) and induce them to shift into an antiaging mode that emphasizes preservation of the organism over such "luxuries" as growth and reproduction.



TERESE WINSLOW

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gest that primates respond to caloric restriction almost identically to rodents, which makes us more optimistic than ever that CR mimetics could help people.

The monkey projects—initiated by our group at the National Institute on Aging in the late 1980s and by a separate team at the University of Wisconsin–Madison in the early 1990s—demonstrate that, compared with control animals that eat normally, caloric-restricted monkeys have lower body temperatures and levels of the pancreatic hormone insulin, and they retain more youthful levels of certain hormones (such as DHEAS, or dehydroepiandrosterone sulfate) that tend to fall with age.

The animals also look better on indicators of risk for age-related diseases. For example, they have lower blood pressure and triglyceride levels (signifying a decreased likelihood of heart disease), and they have more normal blood glucose levels (pointing to a reduced risk for diabetes, which is marked by unusually high blood glucose levels). Further, we have shown that rhesus monkeys kept on caloric restriction for an extended time (nearly 15 years) have less chronic disease, just as the risk data suggested. They and the other monkeys must be followed still longer, however, before we will know whether low food intake can increase both average and maximum life spans in monkeys: rhesus monkeys typically live about 24 years and sometimes up to 40; squirrel monkeys typically live about 19 years but may live for 28.

The Journey Starts

BY 1995 WE WANTED to know how the many physiological and biochemical changes induced by caloric restriction led to delaying aging in mammals. We suspected that changes in cellular metabolism would be key. By "metabolism" we mean the uptake of nutrients from the blood and their conversion to energy usable for cellular activities. We focused on metabolism in part because the benefits of caloric restriction clearly depend on reducing the overall amount or temporal pattern of fuel coming into the body for processing. Also, caloric restriction affects the aging of a wide variety of tissues, which implies that it alters biological processes carried out by all cells. Few processes are more fundamental than metabolism.

If 2DG could mimic caloric restriction in animals, perhaps it would do the same for people.

We specifically wondered whether changes related to metabolism of the sugar glucose would account for the benefits. Glucose, which forms when the body digests carbohydrates, is the primary source of energy in the body—that is, it is the main material used by cells for making ATP, or adenosine triphosphate, the molecule that directly powers most cellular activities. We also wanted to know whether alterations in the secretion and activity of insulin, which influences glucose use by cells, would be important. Insulin is secreted as glucose levels in the blood rise after a meal, and it serves as the key that opens cell "doors" to the sugar. We concentrated on glucose and insulin because reductions in their levels and increases in cellular sensitivity to insulin are among the most consistent hallmarks of caloric restriction in both rodents and primates, occurring very soon after restriction is begun.

Others began publishing data showing that metabolic processes involving glucose and insulin influence life span. For instance, a number of investigations achieved remarkable extensions of life span in nematode worms by mutating genes similar to those involved in molecular responses to insulin in mammals. More recently researchers have found that lowered intake of glucose or disruption of glucose processing can extend life span in yeast. And in fruit flies, genes involved in metabolism, such as INDY (I'm Not Dead Yet), have been implicated in life-span control.

An "Aha!" Moment

AROUND THE TIME the nematode work came out, we began to scour the scientific literature for ways to manipulate insulin secretion and sensitivity without causing diabetes or its opposite, hypoglycemia. Our search turned up studies from the 1940s and 1950s mentioning a compound called 2-deoxy-D-glucose (2DG) that was being tested in rodents for treating cancer but that also reportedly lowered insulin levels in the blood. As we perused the literature further, we had a true "aha!" moment.

The compound apparently reproduced many classic responses to caloric restriction—among them reduced tumor growth, lowered temperature, elevated levels of glucocorticoid hormones and reduced numbers of reproductive cycles. If 2DG really could mimic many aspects of caloric restriction in animals, we thought, perhaps it would do the same for people.

While we were planning our first studies of 2DG, we scanned the literature for details of how it works at the molecular level, learning that it disrupts the functioning of a key enzyme involved in processing glucose in cells. The compound structurally resembles glucose, so it enters cells readily. It is also altered by an enzyme that usually acts on glucose itself. But the enzyme that completes the next of several steps involved in glucose processing essentially chokes on the in-

THE AUTHORS

MARK A. LANE, DONALD K. INGRAM and *GEORGE S. ROTH* researched caloric restriction for many years at the National Institute on Aging of the National Institutes of Health. Lane is now a project manager at Merck in Rahway, N.J., and continues to collaborate with Ingram and Roth as a guest investigator at the NIA. Ingram is chief of the Behavioral Neuroscience Section at the institute's Laboratory of Experimental Gerontology. Roth, who spent nearly 30 years as a full-time researcher at the NIA, is now a senior guest scientist there. He is also chief executive officer of GeroSciences, a biotechnology venture devoted to antiaging strategies.

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CALORIC RESTRICTION'S VARIED EFFECTS

CALORIE-RESTRICTED MONKEY (*left*) is shorter and leaner than its nonrestricted counterpart (*right*).

RODENTS AND MONKEYS on caloric restriction differ from their more abundantly fed counterparts in many ways, some of which are listed below (*1–3*). Although the influence of these shared changes on aging remains to be clarified, the close similarities in the responses of rodents and monkeys encourage hope that the health-promoting and antiaging effects long seen in rodents (*1–4*) are universal among mammals, including humans. If so, caloric-restriction mimetics should help people live well longer. The effects marked by capsules (*below*) have been reproduced in rats by the compound 2DG.

1 EFFECTS INDICATIVE OF ALTERED GROWTH, DEVELOPMENT OR METABOLISM

- Lower body temperatures
- Later sexual maturation
- Later skeletal maturation

2 EFFECTS INDICATIVE OF IMPROVED HEALTH

- Lower weight
- Less abdominal fat

3 EFFECTS INDICATIVE OF REDUCED RISK FOR AGE-RELATED DISEASES (SUCH AS DIABETES AND HEART DISEASE)

- Greater sensitivity to insulin
- Lower fasting insulin levels
- Lower fasting glucose levels
- Lower cholesterol and triglyceride levels
- Lower insulinlike growth factor 1 levels
- Higher levels of "good" (HDL) cholesterol
- Slower decline in levels of the hormone DHEAS

4 EFFECTS FOUND IN RODENTS BUT STILL UNDER INVESTIGATION IN MONKEYS

- Later onset of age-related diseases (including cancer)
- More cell suicide (which may help limit tumor growth)
- Longer average life span
- Longer maximum life span (a strong sign of slowed aging)

termediate produced from 2DG. When it tries to act on this intermediate, it fails; in addition, its ability to act on the normal glucose intermediate becomes impaired [*see box on page 38*].

The net result is that cells make smaller amounts of glucose's by-products, just as occurs when caloric restriction limits the amount of glucose going into cells. Certain of these products serve as the raw material for the ATP-making machinery, which is composed of a series of protein complexes located in intracellular compartments called mitochondria. Deprived of this raw material, the machinery makes less ATP. In essence, 2DG tricks the cell into a metabolic state similar to that seen during caloric restriction, even though the body is taking in normal amounts of food. As long as the amount of ATP made meets the minimum requirements of cells, this diminished operation of the ATP-making machinery is apparently beneficial.

Why might reduced functioning of the ATP-producing machinery help combat aging? We can't say with certainty, but we have some ideas. A long-standing theory of aging blames the production of molecules called free radicals. The lion's share of free radicals in the body are emitted as the ATP-making machinery operates. Over time these highly reactive molecules are thought to cause permanent damage to various parts of cells, including the protein complexes responsible for generating ATP. Perhaps by reducing the rate of ATP production, 2DG and caloric restriction slow the rate at which free radicals form and disrupt cells.

The lack of glucose's by-products might retard aging in another way as well. Certain of those substances help to induce cells in the pancreas to secrete insulin after an organism eats. Reductions in the amount of those by-products would presumably limit insulin secretion and thereby minimize insulin's unwanted actions in the body. Aside from indirectly promoting excessive operation of the ATP-making machinery and thus boosting free-radical production, insulin can contribute to heart disease and to undesirable cell proliferation.

We also suspect that cells interpret reduced levels of raw materials for the ATP-making machinery as a signal that food supplies are scarce. Cells may well respond to that message by switching to a self-protective mode, inhibiting activities not needed for cell maintenance and repair—such as reproduction—and pouring most of their energy into preserving the integrity of their parts. If that idea is correct, it could explain why caloric restriction has been shown to increase production of substances that protect cells from excess heat and other stresses.

This adoption of a self-preservation mode would mirror changes that have been proposed to occur on an organismic level in times of food scarcity. In the generally accepted "disposable soma" theory of aging, Thomas Kirkwood of the University of Newcastle in England has proposed that organisms balance the need to procreate against the need to maintain the body, or soma. When resources are plentiful, organisms can afford both to maintain themselves and to grow and reproduce. But when food is

STUART BRADFORD; NATIONAL INSTITUTE ON AGING (*photographs*)

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limited, the body invokes processes that inhibit growth and reproduction and takes extra care to preserve the soma.

Recent research has indicated another potential pathway for mimicking CR. A National Institute on Aging group led by R. Michael Anson showed that a regimen of intermittent fasting—in which mice were allowed free access to food on alternating days—resulted in beneficial effects similar to those of caloric restriction, including reduced serum glucose and insulin levels and increased resistance of neurons in the brain to toxic stresses. Surprisingly, the food intake and body weight of Anson's mice did not diverge substantially from control mice that had unlimited access to food. These data suggest that an absolute reduction in caloric intake may not underlie all of CR's effects; rather, hormonal changes related to the stress of intermittent fasting may play an important role.

Testing Begins

IN OUR FIRST experiments on 2DG's effectiveness, we delivered low doses to rats by adding it to their feed for six months. The treatment moderately reduced fasting blood glucose levels (measured after food was removed for 12 hours), body weight and temperature and robustly reduced fasting insulin levels—findings consistent with the actions of caloric restriction itself. Interestingly, after an initial adjustment to the novel diet, the 2DG group did not eat significantly less food than the controls. Thus, these exciting preliminary analyses revealed that it was possible to mimic at least some sequelae of caloric restriction without reducing food intake.

Shortly after we published these results, in 1998, other groups began identifying more ways that 2DG imitates caloric restriction. We are in the midst of conducting long-term rodent trials of 2DG. Initial results confirm our previous findings that 2DG slightly reduces blood glucose and body temperature. We also examined whether 2DG reduces the incidence of cancer and increases life span when fed to animals at low doses from the time they are weaned until they die. Contrary to our expectations, the highest dose of 2DG in this experiment did not extend life span. In fact, there was some evidence of early deaths in this group, apparently from toxicity. Interestingly, a lower dose, which had also resulted in some biological effects similar to CR in our early tests, did not show a statistically significant effect on average or maximal life span.

The work so far clearly provides a "proof of concept" that inhibiting glucose metabolism can re-create many effects of caloric restriction. Regrettably, 2DG has a fatal flaw preventing it from being a "magic pill." Though safe at certain low levels, it apparently becomes toxic for some animals when the amount delivered is raised just a bit or given over long periods. The narrowness of the safety zone separating helpful and toxic doses would bar it from human use. We hope this is not a general feature of CR mimetics.

Moving On

ASSUMING OUR long-term studies confirm that inhibiting metabolism can retard aging, the task becomes finding other substances that yield 2DG's benefits but are safer over a broader range of doses and delivery schedules. Several candidates seem promising in early studies, including iodoacetate, being investigated by Mark P. Mattson's group at the NIA's Laboratory of Neurosciences. In animals, this agent appears to protect brain cells from assaults by toxic substances, just as 2DG and caloric restriction do. Treatment with antidiabetic medications that enhance cellular sensitivity to insulin might be helpful as well, as long as the amounts given do not cause blood glucose levels to fall too low.

The task becomes finding other substances that yield 2DG's benefits but are safer.

A great deal of research implicates glucose metabolism in regulating life span, yet other aspects of metabolism can also change in reaction to caloric restriction. When the body cannot extract enough energy from glucose in food, it may shift to breaking down protein and fat. Pharmaceuticals that targeted these processes might serve as CR mimetics, either alone or in combination with drugs that intervene in glucose metabolism. Some compounds that act in those pathways have already been identified, although researchers have not yet assessed their potential as CR mimetics. Drugs that replicate only selected effects of caloric restriction could have a role to play as well. In theory, antioxidant vitamins might fit that bill. Research conducted to date, however, indicates that this particular intervention probably will not extend longevity.

Unlike the multitude of elixirs being touted as the latest antiaging cure, CR mimetics would alter fundamental processes that underlie aging. We aim to devise compounds that fool cells into activating maintenance and repair activities that lead to greater health and longevity of the organism. If scientists can develop agents that offer the benefits of 2DG without its drawbacks, they will finally enable people to have their cake—a longer, healthier life—and eat it, too. SA

MORE TO EXPLORE

2-Deoxy-D-Glucose Feeding in Rats Mimics Physiological Effects of Caloric Restriction. Mark A. Lane, George S. Roth and Donald K. Ingram in *Journal of Anti-Aging Medicine,* Vol. 1, No. 4, pages 327–337; Winter 1998.

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A scientific position statement on human aging mentioned at the start of this article is available at **www.sciam.com/agingstatement.cfm**

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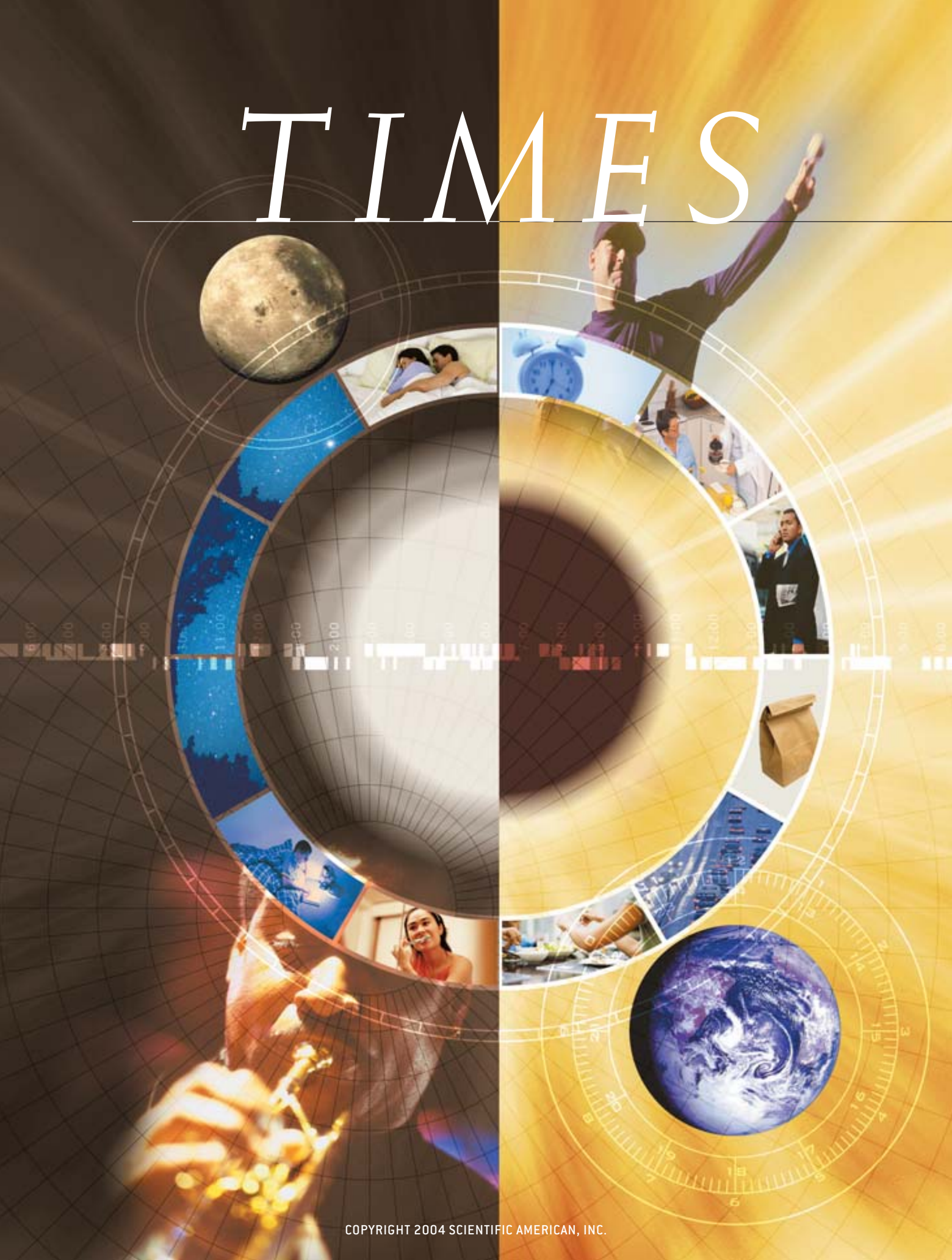
TIMES



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OF OUR LIVES

Whether they're counting minutes or years, biological clocks keep our brains and bodies on time, perhaps even on schedule for death

By Karen Wright

The late biopsychologist John Gibbon called time the "primordial context": a fact of life that has been felt by all organisms in every era. For the morning glory that spreads its petals at dawn, for geese flying south in autumn, for locusts swarming every 17 years and even for lowly slime molds sporing in daily cycles, timing is everything. In human bodies, biological clocks keep track of seconds, minutes, days, months and years. They govern the split-second moves of a tennis serve and account for the trauma of jet lag, monthly surges of menstrual hormones and bouts of wintertime blues. Cellular chronometers may even decide when your time is up. Life ticks, then you die.

The pacemakers involved are as different as stopwatches and sundials. Some are accurate and inflexible, others less reliable but subject to conscious control. Some are set by planetary cycles, others by molecular ones. They are essential to the most sophisticated tasks the brain and body perform. And timing mechanisms offer insights into aging and disease. Cancer, Parkinson's disease, seasonal depression and attention-deficit disorder have all been linked to defects in biological clocks.

The physiology of these timepieces is not completely understood. But neurologists and other clock researchers have begun to answer some of the most pressing questions raised by human experience in the fourth dimension. Why, for example, a watched pot never boils. Why time flies when you're having fun. Why all-nighters can give you indigestion, and why people live longer than hamsters. It's only a matter of time before clock studies resolve even more profound quandaries of temporal existence.

If this article intrigues you, the time you spend reading it will pass quickly. It'll drag if you get bored. That's a quirk of a "stopwatch" in the brain—the so-called interval timer—that marks time spans of seconds to hours. The interval timer helps you figure out how fast you have to run to catch a baseball. It tells you when to clap to your favorite song. It lets you sense how long you can lounge in bed after the alarm goes off.

Interval timing enlists the higher cognitive powers of the cerebral cortex, the brain center that governs perception, memory and conscious thought. When you approach a yellow traffic light, for example, you time how long it has been yellow and compare that with a memory of how long yellow lights usually last. "Then you have to make a judgment about whether to put on the brakes or keep driving," says Stephen M. Rao of the Medical College of Wisconsin.

Rao's studies with functional magnetic resonance imaging (fMRI) have pointed to the parts of the brain engaged in each of those stages. In the fMRI machine, subjects listen to two pairs of tones and decide whether the interval between the second pair is shorter or longer than the interval between the first. The brain structures that are involved in the task consume more oxygen than those that are not involved, and the fMRI scan records changes in blood flow and oxygenation once every 250 milliseconds. "When we do this, the very first structures that are activated are the basal ganglia," Rao says.

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Long associated with movement, this collection of brain regions has recently become a prime suspect in the search for the interval-timing mechanism as well. One area of the basal ganglia, the striatum, hosts a population of conspicuously well-connected nerve cells that receive signals from other parts of the brain. The long arms of these striatal cells are covered with between 10,000 and 30,000 spines, each of which gathers information from a different neuron in another locale. If the brain acts like a network, then the striatal spiny neurons are critical nodes. "This is one of only a few places in the brain where you see thousands of neurons converge on a single neuron," says Warren H. Meck of Duke University.

Striatal spiny neurons are central to an interval-timing theory Meck developed during a decade of research with Gibbon, who worked at Columbia University until his death in 2001. The theory posits a collection of neural oscillators in the cerebral cortex: nerve cells firing at different rates, without regard to their neighbors' tempos. In fact, many cortical cells are known to fire at rates between 10 and 40 cycles per second without external provocation. "All these neurons are oscillating on their own schedules," Meck says, "like people talking in a crowd. None of them are synchronized."

The cortical oscillators connect to the striatum via millions of signal-carrying arms, so the striatal spiny neurons can eavesdrop on all those haphazard "conversations." Then something—a yellow traffic light, say—gets the cortical cells' attention. The stimulation prompts all the neurons in the cortex to fire simultaneously, causing a characteristic spike in electrical output some 300 milliseconds later. This attentional spike acts like a starting gun, after which the cortical cells resume their disorderly oscillations.

But because they have begun simultaneously, the cycles now make a distinct, reproducible pattern of nerve activation from moment to moment. The spiny neurons monitor those patterns, which help them to "count" elapsed time. At the end of a specified interval—when, for example, the traffic light turns red—a part of the basal ganglia called the substantia nigra sends a burst of the neurotransmitter dopamine to the striatum. The dopamine burst induces the spiny neurons to record the pattern of cortical oscillations they receive at that instant, like a flashbulb exposing the interval's cortical signature on the spiny neurons' film. "There's a unique time stamp for every interval you can imagine," Meck says.

Once a spiny neuron has learned the time stamp of the interval for a given event, subsequent occurrences of the event prompt both the "firing" of the cortical starting gun and a burst of dopamine at the *beginning* of the interval [*see top illustration on opposite page*]. The dopamine burst now tells the spiny neurons to start tracking the patterns of cortical impulses that follow. When the spiny neurons recognize the time stamp marking the end of the interval, they send an electrical pulse from the striatum to another brain center called the thalamus. The thalamus, in turn, communicates with the cortex, and the higher cognitive functions—such as memory and decision making—take over. Hence, the timing mechanism loops from the cortex to the striatum to the thalamus and back to the cortex again.

If Meck is right and dopamine bursts play an important role in framing a time interval, then diseases and drugs that affect dopamine levels should also disrupt that loop. So far that is what Meck and others have found. Patients with untreated Parkinson's disease, for example, release less dopamine into the striatum, and their clocks run slow. In trials these patients consistently underestimate the duration of time intervals. Marijuana also lowers dopamine availability and slows time. Recreational stimulants such as cocaine and methamphetamine increase the availability of dopamine and make the interval clock speed up so that time seems to expand. Adrenaline and other stress hormones make the clock speed up, too, which may be why a second can feel like an hour during unpleasant situations. States of deep concentration or extreme emotion may flood the system or bypass it altogether; in such cases, time may seem to stand still or not exist at all. Because an attentional spike initiates the timing process, Meck thinks people with attention-deficit hyperactivity disorder might also have problems gauging the true length of intervals.

The interval clock can be trained to greater precision. Musicians and athletes know that practice improves their timing; ordinary folk can rely on tricks such as chronometric counting ("one one-thousand") to make up for the mechanism's deficits. Rao forbids his subjects from counting in experiments because it activates brain centers related to language as well as timing. But counting works, he says—well enough to expose

> "There's a **unique time stamp** for every interval you can imagine." —*Warren H. Meck, Duke University*

Overview/*Body Clocks*

- In the brain, a "stopwatch" can track seconds, minutes and hours.
- Another timepiece in the brain, more a clock than a stopwatch, synchronizes many bodily functions with day and night. This same clock may account for seasonal affective disorder.
- A molecular hourglass that governs the number of times a cell can divide might put a limit on longevity.

PAGE 42: TOM DRAPER DESIGN; NASA/NSSDC [*Earth and moon*]; CORBIS [*baseball pitcher, horn player and breakfast*]; TOMMY FLYNN *Photonica* [*alarm clock*]; JOHN TERRENCE TURNER *Getty Images* [*highway*]; ROBERT DALY *Stone Getty Images* [*dinner table*]; ERICA McCONNELL *Getty Images* [*brushing teeth*]; GEOFF MANASSE *Aurora* [*child reading*]; YOSHINORI WATABE *Photonica* [*night sky*]

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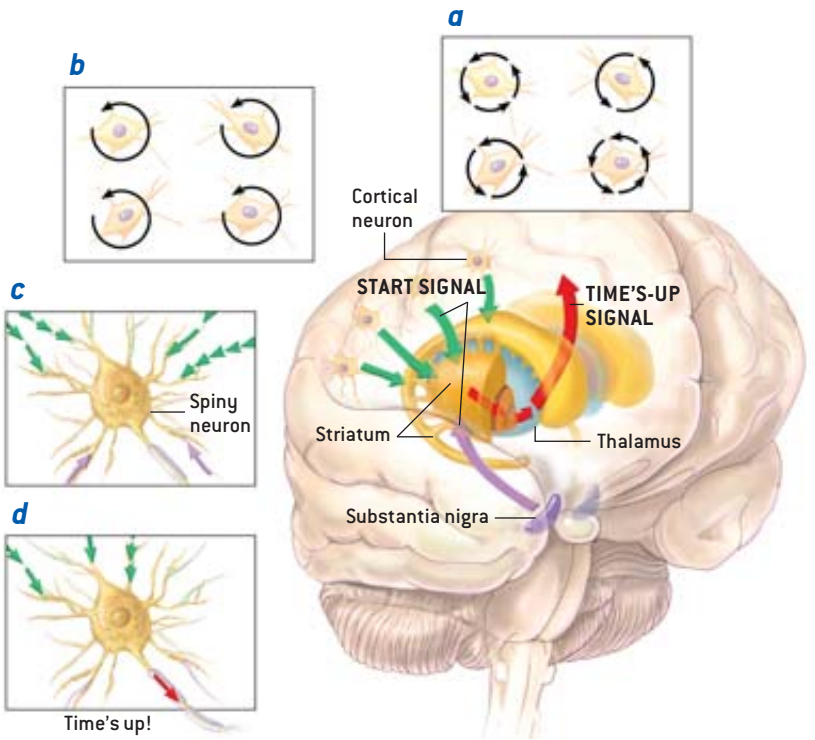
Clocks in the Brain

SCIENTISTS ARE UNCOVERING the workings of two neural timepieces: an interval timer (*top*), which measures intervals lasting up to hours, and a circadian clock (*bottom*), which causes certain body processes to peak and ebb on 24-hour cycles. —*K.W.*

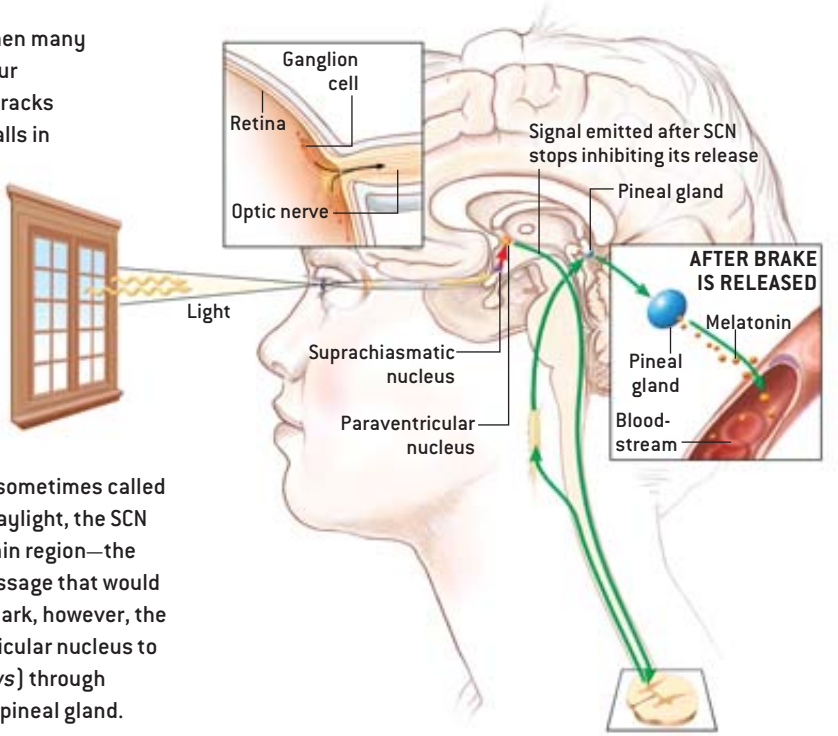


The Interval Timer

ACCORDING TO ONE MODEL, the onset of an event lasting a familiar amount of time (such as the switching on of a four-second yellow traffic light) activates the "start button" of the interval timer by evoking two brain responses. It induces a particular subset of cortical nerve cells that fire at different rates (*a*) to momentarily act together (*b* and *green arrows on brain*), and it prompts neurons of the substantia nigra to release a burst of the signaling chemical dopamine (*purple arrow*). Both signals impinge on spiny cells of the striatum (*c*), which proceed to monitor the overall patterns of impulses coming from the cortical cells after those neurons resume their various firing rates. Because the cortical cells act in synchrony at the start of the interval, the subsequent patterns occur in the same sequence every time and take a unique form when the end of the familiar interval is reached (*d*). At that point, the striatum sends a "time's up" signal (*red arrows*) through other parts of the brain to the decision-making cortex.

The Circadian Clock

DAILY CYCLES OF LIGHT AND DARK influence when many physiological processes that operate on 24-hour cycles will be most and least active. The brain tracks fluctuations in light with the help of ganglion calls in the retina of the eye. A pigment in some of the cells—melanopsin—probably detects light, leading the retinal ganglion cells to send information about its brightness and duration to the suprachiasmatic nucleus (SCN) of the brain. Then the SCN dispatches the information to the parts of the brain and body that control circadian processes. Researchers best understand the events leading the pineal gland to secrete melatonin, sometimes called the sleep hormone (*diagram*). In response to daylight, the SCN emits signals (*red arrow*) that stop another brain region—the paraventricular nucleus—from producing a message that would ultimately result in melatonin's release. After dark, however, the SCN releases the brake, allowing the paraventricular nucleus to relay a "secrete melatonin" signal (*green arrows*) through neurons in the upper spine and the neck to the pineal gland.



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cheaters. "The effect is so dramatic that we can tell whether they're counting or timing based just on the accuracy of their responses."

The Somatic Sundial

ONE OF THE VIRTUES of the interval-timing stopwatch is its flexibility. You can start and stop it at will or ignore it altogether. It can work subliminally or submit to conscious control. But it won't win any prizes for accuracy. The precision of interval timers has been found to range from 5 to 60 percent. They don't work too well if you're distracted or tense. And timing errors get worse as an interval gets longer. "Hence the instruments we all wear on our wrists," Rao notes.

Fortunately, a more rigorous timepiece chimes in at intervals of 24 hours. The circadian clock—from the Latin *circa* ("about") and *diem* ("a day")—tunes our bodies to the cycles of sunlight and darkness caused by the earth's rotation. It helps to program the daily habit of sleeping at night and waking in the morning. But its influence extends much further. Body temperature regularly peaks in the late afternoon or early evening and bottoms out a few hours before we rise in the morning. Blood pressure typically starts to surge between 6 and 7 A.M. Secretion of the stress hormone cortisol is 10 to 20 times as high in the morning as at night. Urination and bowel movements are generally suppressed at night and pick up again in the morning.

The circadian timepiece is more like a clock than a stopwatch because it runs without the need for a stimulus from the external environment. Studies of volunteer cave dwellers and other human guinea pigs have demonstrated that circadian patterns persist even in the absence of daylight, occupational demands and caffeine. And they are expressed in every cell of the body. Confined to a petri dish under constant lighting, human cells still follow 24-hour cycles of gene activity, hormone secretion and energy production. The cycles are hardwired, and they vary by as little as 1 percent: just minutes a day.

But if light isn't required to establish a circadian cycle, it is needed to synchronize the phase of the hardwired clock with natural day and night cycles. Like an ordinary clock that runs a few minutes slow or fast each day, the circadian clock needs to be continually reset to stay accurate. Neurologists have made great progress in understanding how daylight sets the clock. Two clusters of 10,000 nerve cells in the hypothalamus of the brain have long been considered the clock's locus. Decades of animal studies have demonstrated that these centers, each called a suprachiasmatic nucleus (SCN), drive daily fluctuations in blood pressure, body temperature, activity level and alertness. The SCN also tells the brain's pineal gland when to release melatonin, which promotes sleep in humans and is secreted only at night.

In 2002 separate teams of scientists proved that dedicated cells in the retina of the eye transmit information about light levels to the SCN. These cells—a subset of those known as ganglion cells—operate completely independently of the rods and cones that mediate vision, and they are far less responsive to sudden changes in light. That sluggishness befits a circadian system. It would be no good if watching fireworks or going to a movie matinee tripped the mechanism.

But the SCN's role in circadian rhythms is being reevaluated in view of other findings. Until recently, scientists assumed that the SCN somehow coordinated all the individual cellular clocks in the body's organs and tissues. Then, in the mid-1990s, researchers discovered four critical genes that govern circadian cycles in flies, mice and humans. These genes turned up not just in the SCN but everywhere else, too. "These clock genes are expressed throughout the whole body, in every tissue," says Joseph Takahashi of Northwestern University. "We didn't expect that."

Also in 2002 researchers at Harvard University reported that the expression of more than 1,000 genes in the heart and liver tissue of mice varied in regular 24-hour periods. But the genes that showed these circadian cycles differed in the two tissues, and their expression peaked in the heart at different hours than in the liver. "They're all over the map," says Michael Menaker of the University of Virginia. "Some are peaking at night, some in the morning and some in the daytime."

Menaker has shown that specific feeding schedules can shift the phase of the liver's circadian clock, overriding the light-dark rhythm followed by the SCN. When lab rats that usually ate at will were fed just once a day, for example, peak expression of a clock gene in the liver shifted by 12 hours, whereas the same clock gene in the SCN stayed locked in sync with light schedules. It makes sense that daily rhythms in feeding would affect the liver, given its role in digestion. Researchers think circadian clocks in other organs and tissues may respond to other external cues—including stress, exercise, and temperature changes—that occur regularly every 24 hours. No one is ready to dethrone the SCN: its authority over body temperature, blood pressure and other core rhythms is still secure. But this brain center is no longer thought to rule the peripheral clocks with an iron fist. "We have oscillators in our organs that can function independently of our oscillators in our brain," Takahashi says.

The autonomy of the peripheral clocks makes a phenomenon such as jet lag far more comprehensible. Whereas the interval timer, like a stopwatch, can

A virtue of the interval-timing stopwatch is its flexibility. You can start and stop it at will.

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be reset in an instant, circadian rhythms take days and sometimes weeks to adjust to a sudden shift in day length or time zone. A new schedule of light will slowly reset the SCN clock. But the other clocks may not follow its lead. The body is not only lagging; it's lagging at a dozen different paces.

Jet lag doesn't last, presumably because all of those different drummers eventually sync up again. But shift workers, college students and other night owls face a worse chronodilemma. They may be leading a kind of physiological double life. Even if they get plenty of shut-eye by day, their core rhythms are still ruled by the SCN—hence, the core functions continue "sleeping" at night. "You can will your sleep cycle earlier or later," says Alfred J. Lewy of the Oregon Health & Science University. "But you can't will your melatonin levels earlier or later, or your cortisol levels, or your body temperature."

Meanwhile night owls' schedules for eating and exercising could be setting their peripheral clocks to entirely different phases from either the sleep-wake cycle or the light-dark cycle. With their bodies living in so many time zones at once, it's no wonder shift workers have an increased incidence of heart disease, gastrointestinal complaints and, of course, sleep disorders.

A Clock for All Seasons

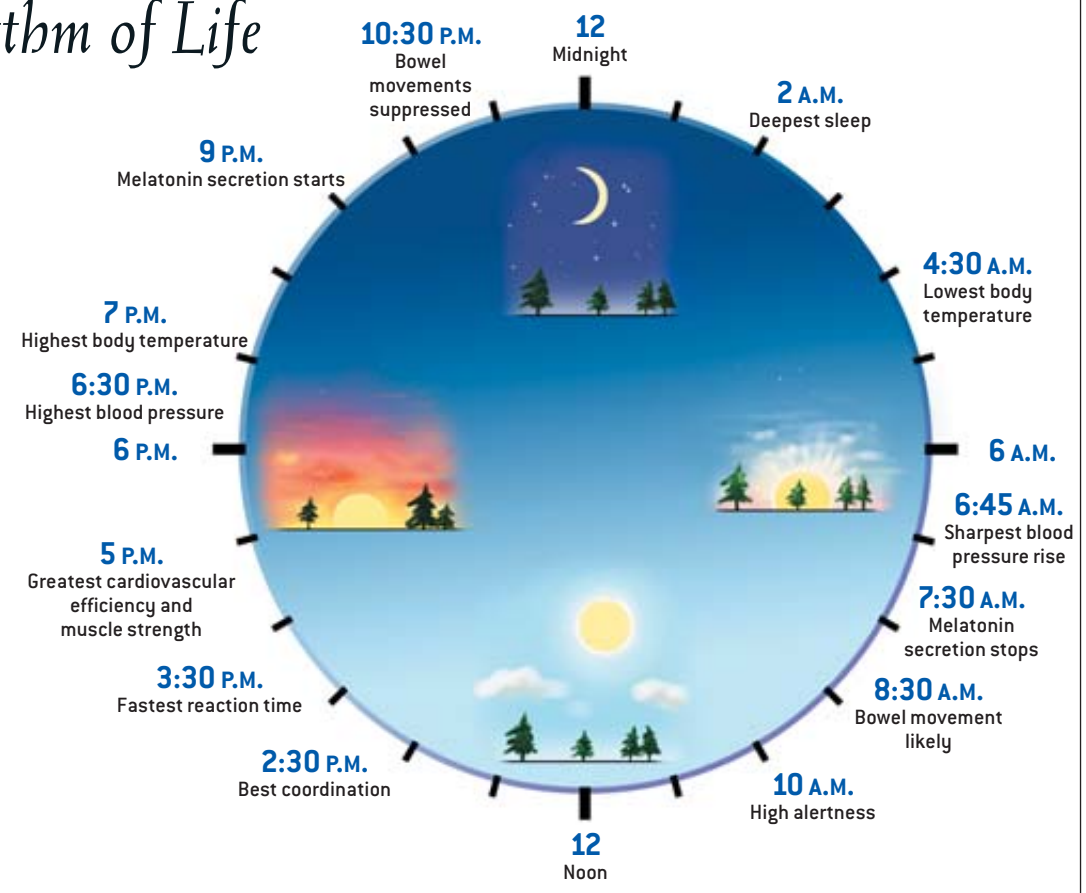
JET LAG AND SHIFT WORK are exceptional conditions in which the innate circadian clock is abruptly thrown out of phase with the light-dark cycles or sleep-wake cycles. But the same thing can happen every year, albeit less abruptly, when the seasons change. Research shows that although bedtimes may vary, people tend to get up at about the same time in the morning year-round—usually because their dogs, kids, parents or careers demand it. In the winter, at northern latitudes, that means many people wake up two to three hours before dawn. Their sleep-wake cycle is several time zones away from the cues they get from daylight.

The mismatch between day length and daily life could explain the syndrome known as seasonal affective disorder, or SAD. In the U.S., SAD afflicts as many as one in 20 adults with depressive symptoms such as weight gain, apathy and fatigue between October and March. The condition is 10 times as common in the north as in the south. Although SAD occurs seasonally, some experts suspect it is actually a circadian problem. Lewy's work suggests that SAD patients would come out of their depression if they could get up at the natural dawn in the winter. In his view, SAD results in part from a failure to adapt sleep-wake cycles to seasonal changes in sunlight. "If we adjust-

CYCLIC EVENTS

The Rhythm of Life

THE CIRCADIAN CLOCK affects the daily rhythms of many physiological processes. This diagram depicts the circadian patterns typical of someone who rises early in the morning, eats lunch around noon and sleeps at night. Although circadian rhythms tend to be synchronized with cycles of light and dark, other factors—such as ambient temperature, meal times, stress and exercise—can influence the timing as well. —*K.W.*



SOURCE: The Body Clock Guide to Better Health, *by Michael Smolensky and Lynne Lamberg, Henry Holt and Company, 2000*

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ed our daily schedules according to the seasons, we might not have seasonal depression," Lewy says. "We got into trouble when we stopped going to bed at dusk and getting up at dawn."

If modern civilization doesn't honor seasonal rhythms, it's partly because human beings are among the least seasonally sensitive creatures around. SAD is nothing compared with the annual cycles other animals go through: hibernation, migration, molting and especially mating, the master metronome to which all other seasonal cycles keep time. It is possible that these seasonal cycles may also be regulated by the circadian clock, which is equipped to keep track of the length of days and nights. Darkness, as detected by the SCN and the pineal gland, prolongs melatonin signals in the long nights of winter and reduces them in the summer. "Hamsters can tell the difference between a 12-hour day, when their gonads don't grow, and a 12-hour-15-minute day, when their gonads do grow," Menaker says.

If seasonal rhythms are so robust in other animals, and if humans have the equipment to express them, then how did we ever lose them? "What makes you think we ever had them?" Menaker asks. "We evolved in the tropics." His point is that many tropical animals don't exhibit dramatic patterns of annual behavior. They don't need them, because the seasons themselves vary so little. Most tropical animals mate without regard to seasons because there is no "best time" to give birth. People, too, are always in heat. As our ancestors gained greater control of their environment over the millennia, seasons probably became an even less significant evolutionary force.

But one aspect of human fertility *is* cyclical: women and other female primates produce eggs just once a month. The clock that regulates ovulation and menstruation is a well-documented chemical feedback loop that can be manipulated by hormone treatments, exercise and even the presence of other menstruating women. But the reason for the specific duration of the menstrual cycle is unknown. The fact that it is the same length as the lunar cycle is a coincidence few scientists have bothered to investigate, let alone explain. No convincing link has yet been found between the moon's radiant or gravitational energy and a woman's reproductive hormones. In that regard, the monthly menstrual clock remains a mystery—outdone perhaps only by the ultimate conundrum, mortality.

Time the Avenger

PEOPLE TEND TO EQUATE aging with the diseases of aging—cancer, heart disease, osteoporosis, arthritis and Alzheimer's, to name a few—as if the absence of disease would be enough to confer immortality. Biology suggests otherwise.

Modern humans in developed countries have a life expectancy of more than 70 years. The life expectancy of the average mayfly, in contrast, is a day. Biologists are just beginning to explore why different species have different life expectancies. If your days are numbered, what's doing the counting?

At a meeting hosted by the National Institute on Aging, participants challenged common assumptions about the factors that determine life span. The answer cannot lie solely with a species' genetics: worker honeybees, for example, last a few months, whereas queen bees live for years. But genetics are important: a single-gene mutation in mice can produce a strain that lives up to 50 percent longer than usual. High metabolic rates can shorten life span, yet many species of birds, which have fast metabolisms, live longer than mammals of comparable body size. And big, slow-metabolizing animals do not necessarily outlast the small ones. The life ex-

SEASONAL CLOCKS

Turn, Turn

MOST ANIMALS experience dramatic seasonal cycles: they migrate, hibernate, mate and molt at specific times of the year (*top four photographs*). The testicles of hamsters, for example, quadruple in size as mating season approaches. These cycles are hardwired: captive ground squirrels continue to hibernate seasonally even when kept in constant temperatures with unvarying periods of light and dark. Likewise, birds in stable laboratory conditions get restless at migration time and keep molting and fattening in yearly cycles.

The only vestige of seasonality in humans may be seasonal affective disorder, a yearly bout of depression that strikes some individuals in winter and can be remedied with light therapy (*bottom photograph*)—or merely by sleeping until the sun comes up. —*K.W.*

TOM DRAPER DESIGN; FRANS LANTING *Minden Pictures* (*swans and butterflies*); GEORGE McCARTHY *Corbis* (*mouse*); MARK JONES *Minden Pictures* (*penguin*); NAJLAH FEANNY (*light therapy*)

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pectancy of a parrot is about the same as a human's. Small breeds of dogs typically live longer than large ones.

Scientists in search of the limits to human life span have traditionally approached the subject from the cellular level rather than considering whole organisms. So far the closest thing they have to a terminal timepiece is the so-called mitotic clock. The clock keeps track of cell division, or mitosis, the process by which a single cell splits into two. The mitotic clock is like an hourglass in which each grain of sand represents one episode of cell division. There seems to be a finite number of times normal cells of the human body can divide. In culture they will undergo 60 to 100 mitotic divisions, then call it quits. "All of a sudden they just stop growing," says John Sedivy of Brown University. "They respire, they metabolize, they move, but they will never divide again."

Cultured cells usually reach this state of senescence in a few months. Fortunately, most cells in the body divide much, much more slowly than cultured cells. But eventually—perhaps after 70 years or so—they, too, can get put out to pasture. "What the cells are counting is not chronological time," Sedivy says. "It's the number of cell divisions."

In 1997 Sedivy reported that he could squeeze 20 to 30 more cycles out of human fibroblasts by mutating a single gene. This gene encodes a protein called p21, which responds to changes in structures called telomeres that cap the end of chromosomes. Telomeres consist of thousands of repetitions of a six-base DNA sequence that does not code for any known protein. Each time a cell divides, chunks of its telomeres are lost. Young human embryos have telomeres between 18,000 and 20,000 bases long. By the time senescence kicks in, the telomeres are only 6,000 to 8,000 bases long.

Biologists suspect that cells become senescent when telomeres shrink below some specific length. Titia de Lange of the Rockefeller University has proposed a new explanation for this link. In healthy cells, she showed, the chromosome ends are looped back on themselves like a hand tucked in a pocket. The "hand" is the last 100 to 200 bases of the telomere, which are single-stranded, not paired like the rest. With the help of more than a dozen specialized proteins, the single-stranded end is inserted into the double strands upstream for protection.

If telomeres are allowed to shrink enough, "they can no longer do this looping trick," de Lange says. Untucked, a single-stranded telomere end is vulnerable to fusion with other single-stranded ends. The fusion wreaks havoc in a cell by stringing together all the chromosomes. That could be why Sedivy's mutated p21 cells died after they got in their extra rounds of mitosis. Other cells bred to ignore short telomeres have turned cancerous. The job of normal p21 and telomeres themselves may be to stop cells from dividing so much that they die or become malignant. Cellular senescence could actually be prolonging human life, rather than spelling its doom. It might be cells' imperfect defense against malignant growth and certain death. "Our hope is that we'll gain enough information from this reductionist approach to help us understand what's going on in the whole person," de Lange comments.

For now, the link between shortened telomeres and aging is tenuous. Most cells do not need to keep dividing to do their job—white blood cells that fight infection and sperm precursors being the obvious exceptions. But many older people do die of simple infections that a younger body could withstand. "Senescence probably has little to do with the nervous system," Sedivy says, because most nerve cells do not divide. "On the other hand, it might very well have something to do with the aging of the immune system."

In any case, telomere loss is just one of the numerous insults cells sustain when they divide, says Judith Campisi of Lawrence Berkeley National Laboratory. DNA often gets damaged when it is replicated during cell division, so cells that have split many times are more likely to harbor genetic errors than young cells. Genes related to aging in animals and people often code for proteins that prevent or repair those mistakes. And with each mitotic episode, the by-products of copying DNA build up in cell nuclei, complicating subsequent bouts of replication.

"Cell division is very risky business," Campisi observes. So perhaps it is not surprising that the body puts a cap on mitosis. And cheating cell senescence probably wouldn't grant immortality. Once the grains of sand have fallen through the mitotic hourglass, there's no point in turning it over again. SA

It is possible that seasonal cycles in animals may be regulated by the circadian clock.

Karen Wright is a science writer based in New Hampshire. Her work is featured in The Best American Science and Nature Writing 2002 *(Mariner Books).*

MORE TO EXPLORE

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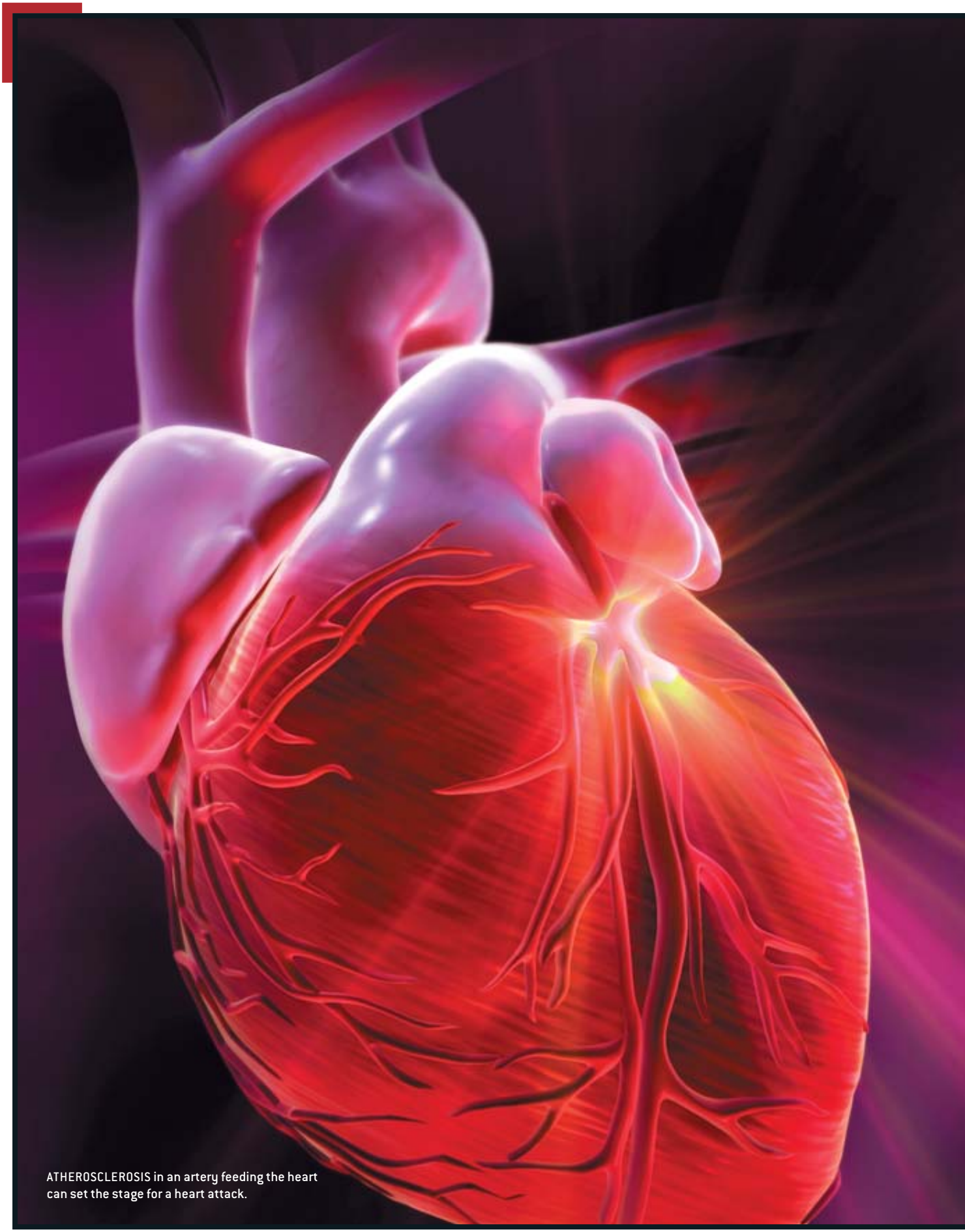

ATHEROSCLEROSIS in an artery feeding the heart can set the stage for a heart attack.

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IT CAUSES CHEST PAIN, HEART ATTACK AND STROKE, LEADING TO MORE DEATHS EVERY YEAR THAN CANCER. THE LONG-HELD CONCEPTION OF HOW THE DISEASE DEVELOPS TURNS OUT TO BE WRONG

the new view of atherosclerosis:

BY PETER LIBBY

JEFF JOHNSON *Hybrid Medical Animation*

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Only a few years ago most physicians would have confidently described atherosclerosis as a straightforward plumbing problem: Fat-laden gunk gradually builds up on the surface of passive artery walls. If a deposit (plaque) grows large enough, it eventually closes off an affected "pipe," preventing blood from reaching its intended tissue. After a while the blood-starved tissue dies. When a part of the cardiac muscle or the brain succumbs, a heart attack or stroke occurs.

Few believe that tidy explanation anymore. Investigations begun more than 20 years ago have now demonstrated that arteries bear little resemblance to inanimate pipes. They contain living cells that communicate constantly with one another and their environment. These cells participate in the development and growth of atherosclerotic deposits, which arise in, not on, vessel walls. Further, relatively few of the deposits expand so much that they shrink the bloodstream to a pinpoint. Most heart attacks and many strokes stem instead from less obtrusive plaques that rupture suddenly, triggering the formation of a blood clot, or thrombus, that blocks blood flow.

Recent research has, moreover, established a key role for inflammation in atherosclerosis. This process—the same one that causes infected cuts to become red, swollen, hot and painful—underlies all phases of the disorder, from the creation of plaques to their growth and rupture. When microbial invaders threaten to hurt us, inflammation (literally meaning "on fire") helps to ward off infection. In the case of atherosclerosis, though, the inflammation proves harmful. Our own defenses bombard us with friendly fire, just as happens in more famously inflammatory conditions, such as rheumatoid arthritis.

This revised conception suggests new ideas for detecting and treating atherosclerosis. It also resolves some disturbing mysteries—notably, why many heart attacks strike without warning and why certain therapies meant to avert heart attacks frequently fail. Society sorely needs advances in prevention, detection and therapy of atherosclerosis. Contrary to public perception, the heart attacks and strokes that result from this condition exceed cancer as a cause of death in industrial nations and are growing more prevalent in developing countries as well.

Overview/*Atherosclerosis*

- Scientists now agree that inflammation fuels the development and progression of atherosclerosis: the dangerous accumulation of fat-laden deposits, or plaques, in the arteries. The old view—that fat builds up on passive arterial walls—does not fit recent evidence.
- Inflammation can also cause certain plaques to rupture. Blood clots tend to form over ruptured plaques and can then occlude arteries, leading to such atherosclerotic complications as heart attack and stroke.
- Excess low-density lipoprotein (LDL), or "bad cholesterol," in the blood can trigger arterial inflammation. And cholesterol-lowering therapies—already cornerstones of treatment for atherosclerosis—can reduce it. Strategies that interfere with inflammation in other ways are under study as well.
- A blood test that detects ongoing inflammation might prove useful as an adjunct to the cholesterol tests that doctors now employ to assess risk for heart attack and stroke.

Igniting Trouble

LACKING TOOLS to describe interactions among cells and molecules, the ancients who first defined inflammation had to focus on what they could see and feel. Today we know that the outward signs reflect a pitched microscopic battle. After sensing (rightly or wrongly) that a microbial attack has begun, certain white blood cells—the immune system's frontline warriors—convene in the apparently threatened tissue. There they secrete chemicals intended to limit any infection. These chemicals include oxidants (able to damage invaders) and signaling molecules, such as proteins called cytokines, that orchestrate the activities of defensive cells. Researchers therefore document an inflammatory response by identifying inflammatory cells or mediators of their activities in a tissue.

The clearest picture of inflammation's role in the onset of atherosclerosis comes from investigations into low-density lipoprotein, a.k.a. bad cholesterol. LDL particles, composed of fatty molecules (lipids) and protein, transport cholesterol (another lipid) from their source in the liver and intestines to other organs. Scientists have long known that although the body needs LDL and cholesterol, excessive amounts promote atherosclerosis. Until recently, however, no one could explain how a surplus leads to plaque formation.

Experiments on cultured cells and animals now indicate that the trouble begins when LDLs from the blood collect in the intima, the part of the arterial wall closest to the bloodstream [*see illustration on page 54*]. At reasonable concentrations in the blood, LDLs can pass in and out of the intima, which consists mainly of the endothelial cells that line vessel walls, the underlying extracellular matrix (connective tissue), and a smat-

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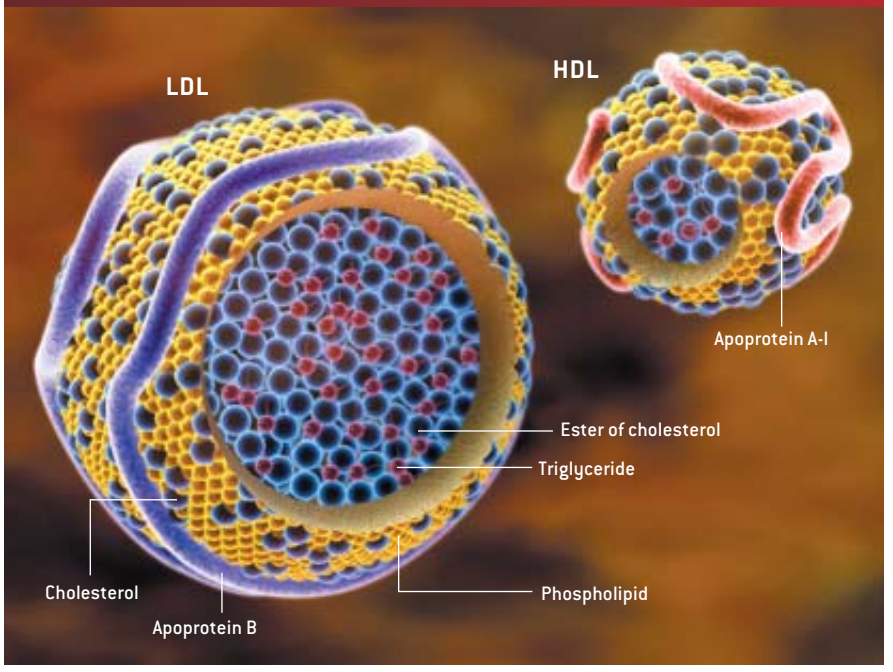
NEW ROLES FOR FAMILIAR ACTORS

POPULAR DESCRIPTIONS of atherosclerosis correctly cast low-density lipoprotein (LDL) as "bad" and high-density lipoprotein (HDL) as "good." Yet these particles (*shown in cutaway views*) fulfill their roles in more ways than scientists once thought.

Lipoproteins transport cholesterol in the bloodstream. LDLs truck it from the liver and intestines to various tissues, which use it to repair membranes or produce steroid hormones. HDLs haul cholesterol to the liver for excretion or recycling. The classic view of how atherosclerosis develops implies that excess LDL promotes the condition by accumulating on vessel walls. More recent work shows that it accumulates *within* vessel walls, where its components become oxidized and altered in other ways; the modified components then incite an inflammatory response that progressively—and dangerously—alters arteries.

Physicians generally explain HDL's protective effects as deriving from its removal of cholesterol from arteries. HDL certainly does that, but new findings indicate it can also combat atherosclerosis with anti-inflammatory action. —*P.L.*



MEDICINE HORSE *Hybrid Medical Animation*

tering of smooth muscle cells (matrix producers). But in excess, LDLs tend to become stuck in the matrix.

As the LDLs accumulate, their lipids undergo oxidation (similar to the processes that rust pipes and spoil butter) and their proteins undergo both oxidation and glycation (binding by sugars). Cells in the vessel wall seem to interpret the changes as a danger sign, and they call for reinforcements from the body's defense system.

In particular, endothelial cells display adhesion molecules on their blood-facing surface. These molecules latch like Velcro onto quiescent inflammatory cells known as monocytes, which normally circulate in the blood. This interaction causes the cells to attach to the artery wall. The modified LDLs also spur the endothelial cells and smooth muscle cells of the intima to secrete chemicals called chemokines, which attract monocytes. Much as hounds track the scent of their prey, the monocytes squeeze between endothelial cells and follow the chemical trail to the intima.

Chemokines and other substances elaborated by the endothelial and smooth muscle cells then induce the monocytes to multiply and mature into active macrophages: fully armed warriors, ready to unleash their various weapons against the body's enemies. These warriors set about clearing perceived invaders from the vessel wall. Reacting to proteins emitted by stimulated endothelial and intimal smooth muscle cells, the macrophages decorate their surface with molecules called scavenger receptors, which capture modified LDL particles and help the macrophages ingest them. The macrophages ultimately become so packed with fatty droplets that they look foamy when viewed under a microscope. Indeed, pathologists refer to the fat-filled macrophages as foam cells.

Just as monocytes follow adhesion molecules and chemokines into the intima, so do T lymphocytes, white blood cells that represent a different branch of the immune system. They also release cytokines that amplify inflammatory activities. Together the foamy macrophages and a lesser number of T lymphocytes compose the so-called fatty streak, a precursor of the complex plaques that later disfigure arteries. Disturbingly, many Americans harbor nascent plaques as early as in their teens.

Fueling Plaque Growth

WHEN AN inflammatory response in, say, a scraped knee successfully blocks an infection, macrophages release molecules that facilitate healing. A "healing" process also accompanies the chronic inflammation that operates in atherosclerosis. But instead of restoring arterial walls to their original state, the process perversely remodels the wall, generating a bigger, more complicated plaque.

In recent years, biologists have learned that macrophages, endothelial cells and smooth muscle cells of the inflamed intima secrete factors that prod smooth muscle cells of the media (the tissue under the intima) to migrate to the top of the intima, replicate and synthesize components of the extracellular matrix. The cells and matrix molecules coalesce into a fibrous covering overlying the original atherosclerotic zone. As this "cap" matures, the zone underneath generally changes somewhat. Most obviously, some fraction of the foam cells

Continued on page 56

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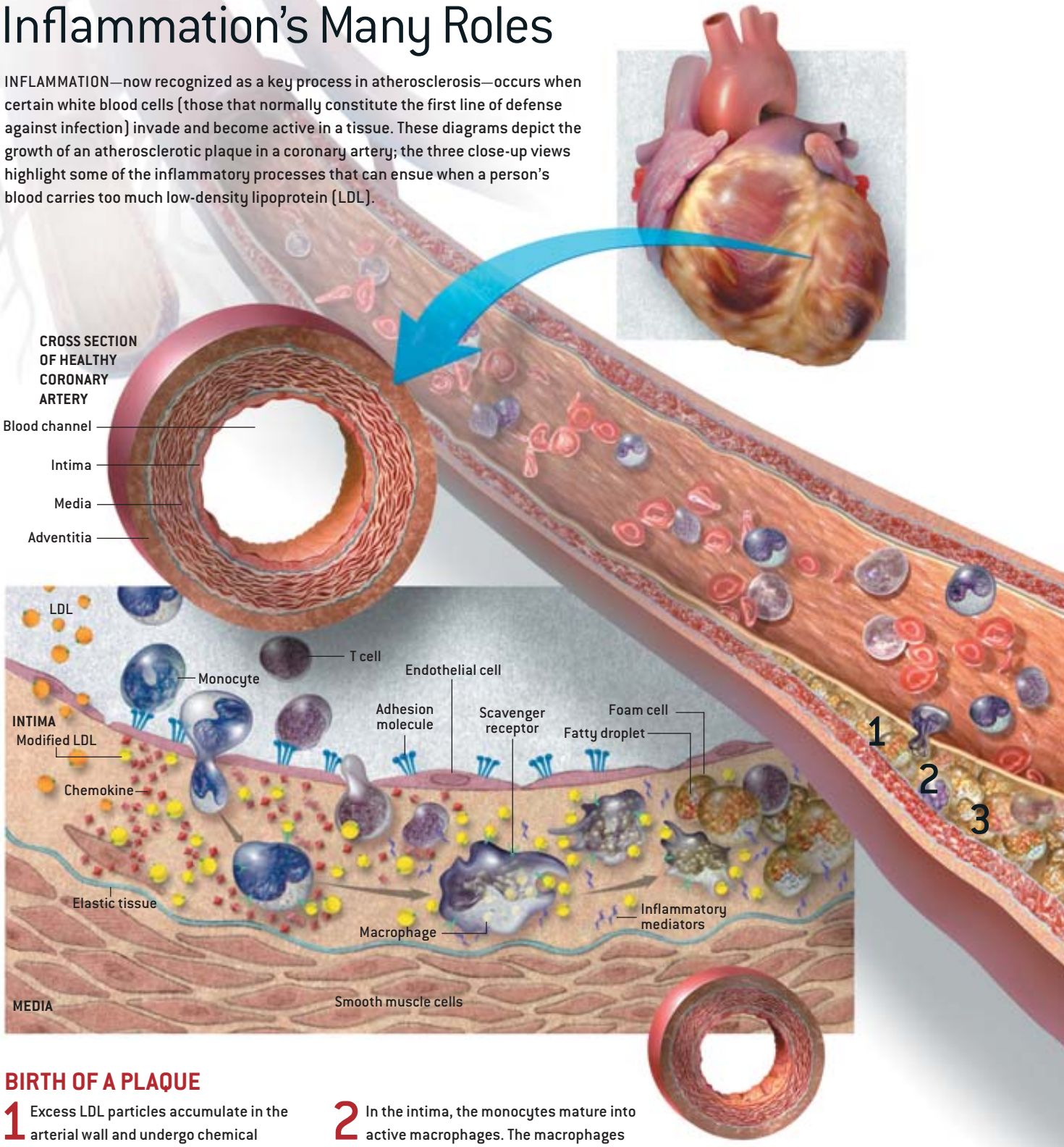
Inflammation's Many Roles

INFLAMMATION—now recognized as a key process in atherosclerosis—occurs when certain white blood cells (those that normally constitute the first line of defense against infection) invade and become active in a tissue. These diagrams depict the growth of an atherosclerotic plaque in a coronary artery; the three close-up views highlight some of the inflammatory processes that can ensue when a person's blood carries too much low-density lipoprotein (LDL).



BIRTH OF A PLAQUE

1 Excess LDL particles accumulate in the arterial wall and undergo chemical alterations. The modified LDLs then stimulate endothelial cells to display adhesion molecules, which latch onto monocytes (central players in inflammation) and T cells (other immune system cells) in the blood. The endothelial cells also secrete chemokines, which lure the snared cells into the intima.

2 In the intima, the monocytes mature into active macrophages. The macrophages and T cells produce many inflammatory mediators, including cytokines (best known for carrying signals between immune system cells) and factors that promote cell division. The macrophages also display so-called scavenger receptors, which help them ingest modified LDLs.

3 The macrophages feast on LDLs, becoming filled with fat droplets. These frothy-looking macrophages (called foam cells) and the T cells constitute the fatty streak, the earliest form of atherosclerotic plaque.

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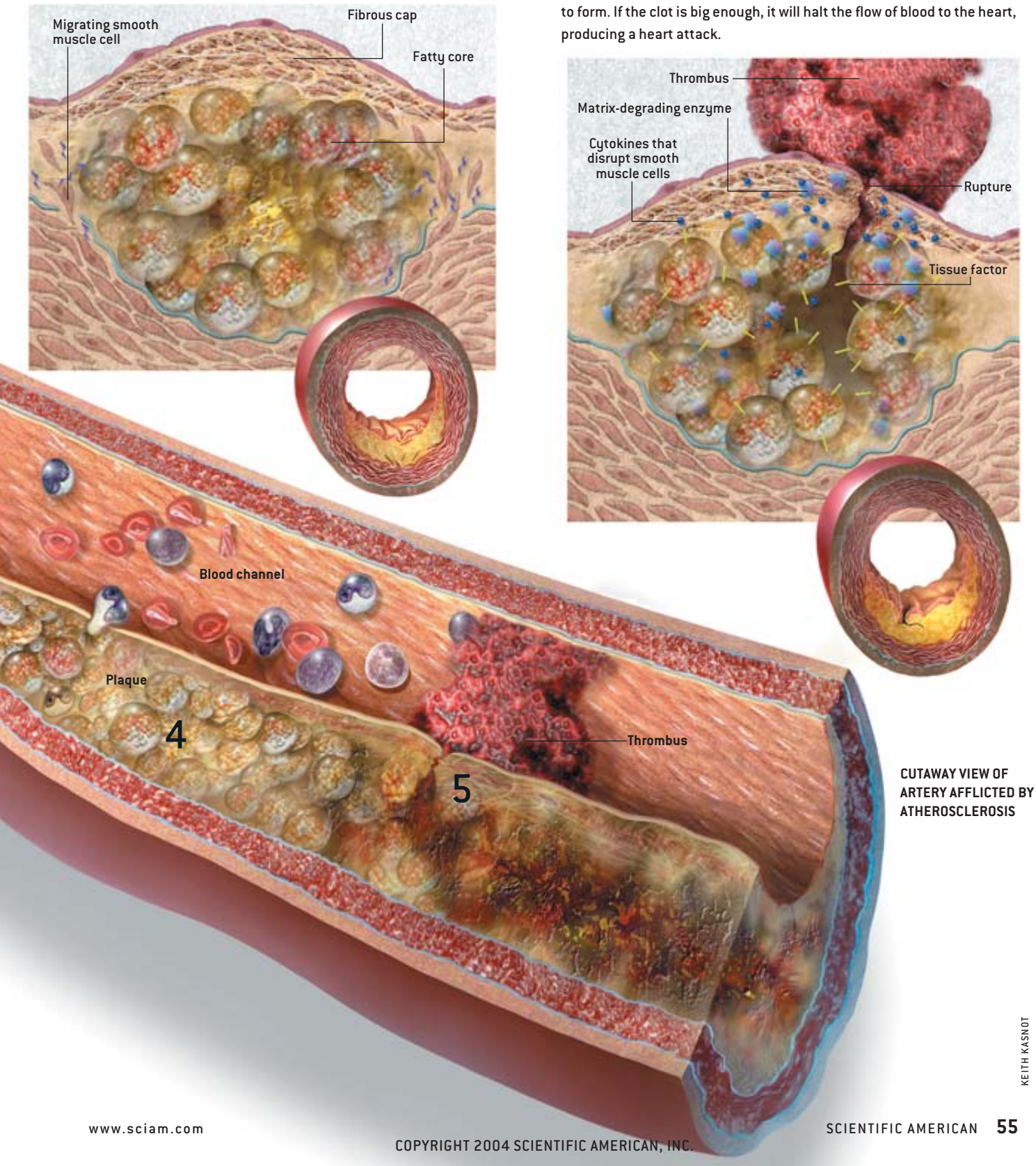
PLAQUE PROGRESSION

4 Inflammatory molecules can promote further growth of the plaque and formation of a fibrous cap over the lipid core. The cap develops when the molecules induce smooth muscle cells of the media to migrate to the top of the intima, multiply and produce a tough, fibrous matrix that glues the cells together. The cap adds to the size of the plaque but also walls it off safely from the blood.

PLAQUE RUPTURE

5 Later, inflammatory substances secreted by foam cells can dangerously weaken the cap by digesting matrix macromolecules and damaging smooth muscle cells, which then fail to repair the cap. Meanwhile the foam cells may display tissue factor, a potent clot promoter. If the weakened plaque ruptures, tissue factor will interact with clot-promoting elements in the blood, causing a thrombus, or clot, to form. If the clot is big enough, it will halt the flow of blood to the heart, producing a heart attack.



CUTAWAY VIEW OF ARTERY AFFLICTED BY ATHEROSCLEROSIS

KEITH KASNOT

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Continued from page 53

die, releasing lipids. For this reason, pathologists denote the region under the cap as the lipid or necrotic core.

Surprisingly, atherosclerotic plaques expand outward during much of their existence, rather than impinging on an artery's blood-carrying channel. This pattern preserves blood flow for quite some time, often for decades. When the plaques do push inward, they restrict the blood channel—a condition called stenosis. Stenosis can impede blood delivery to tissues, especially at moments of greater need, when the arteries would usually expand. When a person exercises or experiences stress, for instance, blood flow through a compromised heart artery can fail to match the increased demand, causing angina pectoris: a feeling of tightness, squeezing or pressure usually under the breastbone. Narrowing in other arteries can cause painful cramping of the calves or buttocks during exertion, symptoms known as intermittent claudication.

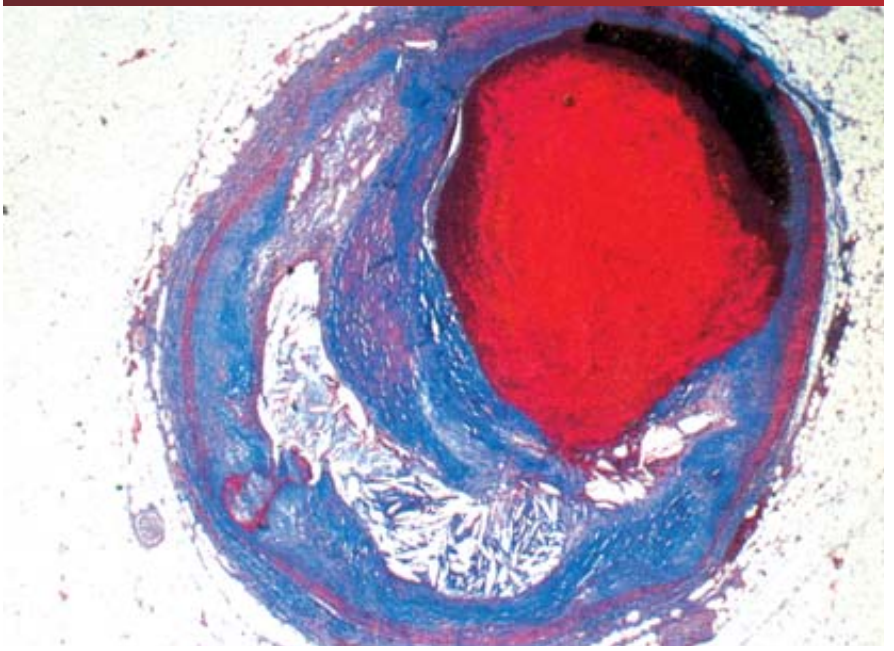
Causing Crises

SOMETIMES A PLAQUE grows so big that it virtually halts blood flow in an artery and generates a heart attack or stroke. Yet only about 15 percent of heart attacks happen in this way. By carefully examining vessel walls of people who died from heart attacks, pathologists have demonstrated that most attacks occur after a plaque's fibrous cap breaks open, prompting a blood clot to develop over the break. The plaques most likely to fracture possess a thinned cap, a large lipid pool and many macrophages, and their vulnerability stems—again—from inflammation.

The integrity of the fibrous covering depends mostly on steel-strong collagen fibers made by smooth muscle cells. When something causes inflammation to flare in a relatively quiet plaque, mediators of the process can compromise the cap in at least two ways. My laboratory has shown that these inflammatory mediators can stimulate macrophages to secrete enzymes that degrade collagen and that they can inhibit smooth muscle cells from extruding the fresh collagen required to repair and maintain the cap.

AN INSIDE VIEW

THE BLOOD CLOT, or thrombus (*red*), captured in this micrograph has formed at the site of an atherosclerotic plaque in a coronary artery and has occluded the vessel. Some clots dissolve before they cause a heart attack or stroke, but they can foster trouble in another way—by stimulating plaque expansion.



Clots form when blood seeps through a fissure in the cap and encounters a lipid core teeming with proteins able to facilitate blood coagulation. For example, molecules on T cells in the plaques spur foam cells to manufacture high levels of tissue factor, a potent clot inducer. Circulating blood itself contains precursors of the proteins involved in the cascade of reactions responsible for clot formation. When blood meets tissue factor and other coagulation promoters in a plaque's core, the clotting precursors jump into action. Our bodies produce substances that can prevent a clot from materializing or can degrade it before it causes a heart attack or stroke, but inflamed plaques release chemicals that impede the innate clot-busting machinery.

If a clot does get cleared naturally or with the aid of drugs, the healing process may kick in once again, restoring the cap but also further enlarging the plaque by forming scar tissue. Indeed, considerable evidence suggests that plaques grow in fits and starts, as triggers of inflammation come and go and as clots emerge and dissolve but leave fibrous scars.

The new picture of atherosclerosis explains why many heart attacks seem to come from out of the blue: the plaques that rupture do not necessarily protrude very far into the blood channel and so may not cause angina or appear prominently on images of the channel. The new view also clarifies why therapies that focus on widening the blood passage in semioccluded arteries (balloon angioplasty or insertion of wire-cage stents) or on surgically creating a bypass can ease angina yet frequently fail to prevent a future heart attack. In such cases, the danger may lurk in less occlusive plaques that are more prone to rupturing. Sadly, even when stenosis *is* the problem, arteries treated with traditional stents often become reoccluded—apparently in part because their deployment can elicit a robust inflammatory response. New coated stents that slowly release anti-inflammatory drugs have lessened the return of blockage.

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Beyond Bad Cholesterol

ALTHOUGH LDL frequently sparks the sequence of events I have outlined, scientists have identified several other factors that unequivocally increase a person's risk for atherosclerosis or its complications. Many of these risk factors, and a few still under study, exhibit intriguing inflammatory properties. Yet LDL probably plays an even larger role in initiating and perpetuating atherosclerosis than is generally recognized.

A much repeated statistic says that half of all patients who have angina or have had a heart attack do not have above-average LDL levels—a finding frequently interpreted to mean that in such individuals, LDL exerts no influence on the atherosclerosis at the root of those disorders. But typical LDL levels in Western society exceed by far the body's needs, and even these "average" amounts can promote arterial disease.

Indeed, in response to new data correlating heart health with lipoprotein levels, public health experts have progressively refined the definition of "healthy" LDL levels. Current guidelines elaborated by an expert panel convened in cooperation with the National Institutes of Health explicitly label LDL-cholesterol levels below 100 milligrams per deciliter of blood (mg/dL) as optimal. They also suggest considering drug treatment earlier than before—at 130 mg/dL instead of 160—for certain people with multiple risk factors. For adults with a relatively low risk of heart disease, the guidelines recommend (as before) initiating lifestyle changes—diet and exercise—at 160 mg/dL and considering drug treatment at 190 mg/dL. Since these guidelines were issued in 2001, data emerging from large, thorough trials justify an even more aggressive stance. Revised guidelines and reassessment of treatment goals for LDL cholesterol are likely to result.

Investigators have yet to explore the connections between other risk factors and inflammation with the intensity accorded to LDL, but they have uncovered suggestive links. Diabetes, for instance, elevates glucose levels in the blood; this sugar can enhance the glycation, and thus the inflammatory properties, of LDL. Smoking causes oxidants to form and might hasten the oxidation of LDL's constituents, thereby fostering arterial inflammation even in individuals with average LDL levels. Obesity contributes to diabetes and vascular inflammation. High blood pressure may not exert direct inflammatory effects, but a hormone partly responsible for much human hypertension—angiotensin II—appears to incite inflammation as well; elevated levels of this hormone, therefore, might give rise to hypertension and atherosclerosis simultaneously.

Conversely, high-density lipoprotein (HDL) seems beneficial; as levels of this "good cholesterol" decline, the likelihood of suffering a heart attack goes up. Accordingly, to fine-tune estimates of cardiovascular risk, many physicians today measure not only levels of LDL in the blood but also the level of HDL and the ratio of LDL (or LDL plus its various relatives) to HDL. HDL may achieve its beneficial effects in part by reducing inflammation: along with cholesterol, it can transport antioxidant enzymes able to break down oxidized lipids. Strategies to elevate HDL with drugs will require human testing to prove clinical benefit. But exercise and weight control can raise HDL and reduce cardiovascular risk—lifestyle changes that the public can adopt today without waiting for studies or pharmaceuticals.

Given inflammation's usual responsibility in the body—blocking and eliminating infectious agents—biologists have naturally looked at whether arterial infections might contribute to inflammation in the arteries. Recent work suggests that atherosclerosis can develop in the absence of infection. Nevertheless, circumstantial evidence suggests that certain microorganisms, such as herpesviruses and the bacterium *Chlamydia pneumonia* (a frequent cause of respiratory infections), could well induce or aggravate atherosclerosis at times. *C. pneumonia,* for instance, appears in many atherosclerotic plaques, and its constituents can evoke inflammatory responses by macrophages and by vascular endothelial and smooth muscle cells.

Infections might also act from a distance, in what I call an echo effect. When the body fights infections, inflammatory mediators can escape into the blood and travel to distant sites. These substances can, in theory, stimulate the white cells in atherosclerotic plaques, thereby prompting plaque growth or rupture. Clinical trials to see whether limited courses of antibiotics will prevent recurrent heart attacks are under way. One such study has already shown, however, that anti-

The outward signs of inflammation reflect struggle on a microscopic battlefield.

THE AUTHOR

PETER LIBBY, who earned his M.D. from the University of California, San Diego, is chief of cardiovascular medicine at Brigham and Women's Hospital, Mallinckrodt Professor of Medicine at Harvard Medical School, and co-editor of *Heart Disease,* a classic cardiology textbook (W. B. Saunders, 2001). He regards "lifestyle modification as the cornerstone of cardiovascular prevention" and practices what he preaches by running recreationally, albeit, he says, more avidly than swiftly.

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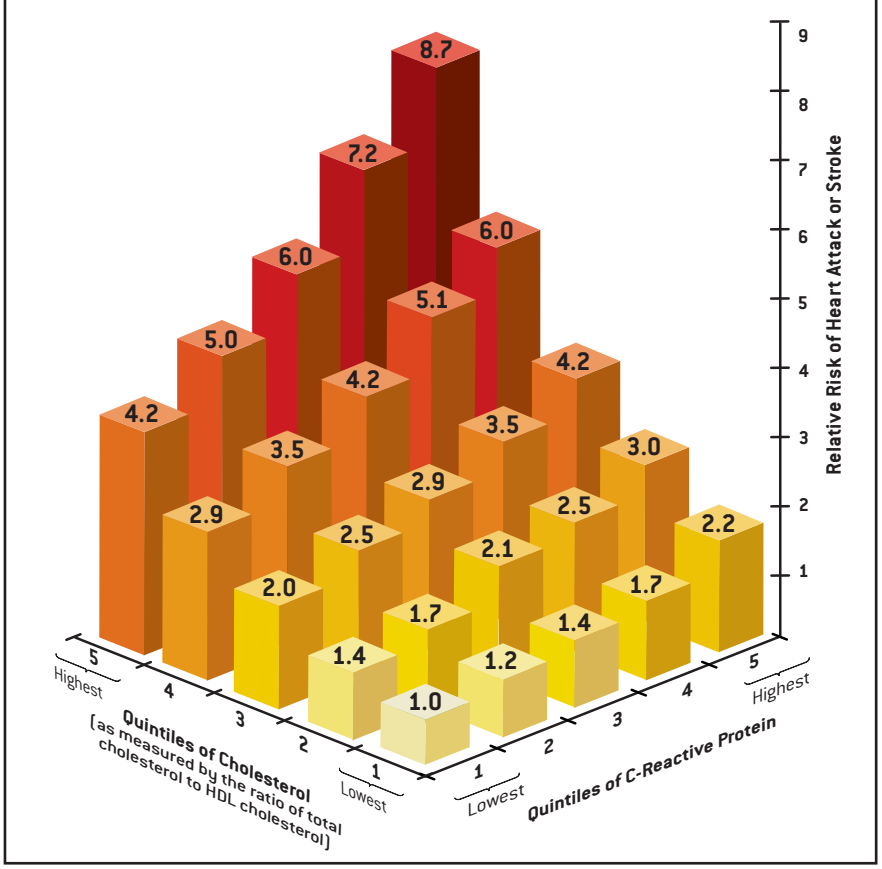
A TELLING TEST

IN DECIDING WHETHER a patient requires therapy to prevent an atherosclerosis-related heart attack or stroke, physicians usually rely heavily on measurements of cholesterol in the person's blood. But that approach misses a great many vulnerable individuals. Several studies suggest that measuring blood concentrations of C-reactive protein—a marker of inflammation—could add useful information. Indeed, in one recent report, Paul M. Ridker of Brigham and Women's Hospital demonstrated that examining both C-reactive protein levels (which cannot be predicted from cholesterol measures) and cholesterol levels provides a more accurate indication of risk than assessing cholesterol alone (*graph*).

Ridker grouped cholesterol levels in the general adult population into five progressively rising ranges (quintiles) and, separately, divided C-reactive protein levels into quintiles. Then he determined the relative risk faced by people having different combinations of cholesterol and C-reactive protein values. That is, he assigned a danger level of 1 to individuals whose cholesterol and C-reactive values both fell in the lowest quintile (*front corner*) and calculated how much that risk multiplied in adults having other permutations of cholesterol and C-reactive protein measurements.

He found that high C-reactive protein values signify markedly elevated risk for heart attack or stroke even in individuals with seemingly reassuring cholesterol values. For instance, people with average (third-quintile) cholesterol levels and the highest C-reactive protein levels face much the same peril as those who have the highest cholesterol and lowest C-reactive protein levels. And subjects having the highest values for both cholesterol and C-reactive protein confronted the greatest risk of all. Encouraged by such results, researchers have begun a large study assessing whether basing treatment decisions on combined C-reactive protein and cholesterol testing will save lives. —*P.L.*



biotics do not forestall recurrences in heart attack survivors.

Reducing Danger

INFLAMMATION'S essential role in atherosclerosis implies that anti-inflammatory medicines might slow this disease, and some (including aspirin) are already in use or under study. But logic and the investigations conducted so far suggest a need to look elsewhere as well.

Aspirin belongs to the class of drugs known as NSAIDs (nonsteroidal anti-inflammatory drugs), a group that also claims such popular painkillers as ibuprofen and naproxen. Like other NSAIDs, aspirin can block the formation of certain lipid mediators of inflammation, including the prostaglandins, which generate pain and fever. Strong data from clinical trials indicate that aspirin shields against heart attacks and, in some patients, against ministrokes. But the low doses that afford this protection probably reduce the clotting propensity of blood platelets instead of quieting the inflammation.

Scientists have little clinical data relating to the effects of other NSAIDs on atherosclerosis, and there is evidence that selective inhibitors of the prostaglandin-producing enzyme COX-2 might actually enhance thrombus development in some patients. Cortisone and related steroids could prove too toxic for long-term use, and no data support their utility in reducing atherosclerotic complications.

Even if anti-inflammatory drugs proved effective, they might have to be taken for years to keep atherosclerosis at bay. That prospect worries me, because ongoing interference with inflammation could increase the risk of infection. One day someone might devise a way to halt the chronic, destructive inflammation of atherosclerosis without undermining overall immunity. But I suspect that a more practical strategy would concentrate on defusing the triggers at the root of arterial inflammation.

Fortunately, some means are at hand already. A heart-healthy diet, regular exercise and, for obese individuals, weight loss can reduce the risk of a heart attack and combat diabetes. In addition, since

NINA FINKEL; SOURCE: "HIGH-SENSITIVITY C-REACTIVE PROTEIN: POTENTIAL ADJUNCT FOR GLOBAL RISK ASSESSMENT IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE," BY PAUL M. RIDKER IN *CIRCULATION*, VOL. 103, PAGES 1813–1818; APRIL 3, 2001

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1994 several impeccably executed trials have established beyond a doubt that lipid-lowering drugs can reduce the likelihood of atherosclerotic complications and can prolong life in individuals with a broad range of risk levels. Researchers have not yet nailed down the mechanism behind the success of the lipid-lowering drugs, which do not seem to reduce arterial stenosis substantially. But studies of cells, whole animals and humans suggest that lipid lowering might help by limiting inflammation, thereby minimizing plaque buildup and making existing plaques less likely to rupture.

Recent analyses of the statins (widely prescribed lipid-controlling drugs) support this notion. They confirm that the drugs can decrease inflammation in patients. Experiments on isolated cells and laboratory animals indicate, too, that the drugs' anti-inflammatory effects may not depend entirely on changing the concentrations of lipids in the blood. Statins—which decrease the levels of LDL and related bad lipids by increasing their disposal in the body—also limit the availability of chemicals that enable cells to respond to inflammatory mediators.

Experimental drugs that aim at other risk factors for heart disease and stroke might exert useful anti-inflammatory effects as well. Agents that raise levels of HDL or limit the action of angiotensin II come to mind. But treatment with antioxidant vitamins has proved disappointing.

No matter how useful a drug is, it will be of no value if it sits unused on pharmacy shelves. Doctors need better ways of detecting dangerous atherosclerosis in the large fraction of people whose lipid levels look too good to justify treatment. Recent findings suggest that blood tests combining lipid testing with monitoring of a substance called C-reactive protein might help improve detection.

Toward Early Detection

THE PRESENCE of C-reactive protein in the blood signifies that inflammation is occurring somewhere in the body; highly elevated levels, even in the presence of LDL values too low to prompt treatment under current guidelines, indicate an increased risk of heart attack or stroke. What is more, in at least one study, delivery of statins to people with below-average LDL concentrations but high C-reactive protein levels reduced the incidence of heart attack relative to the rate in a matched group of patients who received no treatment. Such results need to be confirmed in the much larger trial that is currently under way before doctors can confidently treat patients on the basis of the combined test, although some physicians already incorporate tests of C-reactive protein in their practices. Recent guidelines recommend use of the C-reactive protein test in individuals who fall in the intermediate "gray zone" of traditional clinical criteria—neither high nor low risk. This simple blood test can prompt lifestyle changes and serve as a tiebreaker for decisions on drug therapy.

Noninvasive methods for specifically identifying vulnerable plaques might also help pinpoint individuals who lack strong warning signs but who nonetheless are destined for disaster. Ideas include measuring the heat of blood vessels (because heat typically accompanies inflammation) and altering existing imaging technologies, such as MRI or CT scans, to improve their ability to visualize material inside vessel walls. Geneticists, meanwhile, are hunting for gene variants that render some people more vulnerable to chronic inflammation and to atherosclerosis and its complications so that the individuals most prone to these disorders can seek more aggressive monitoring and treatment.

For most of human history, inflammation's ability to ward off infection outweighed its drawbacks. Today, as we live longer, exercise less, eat too much and smoke, many of us suffer from inflammation's dark side. Scientists continue to pursue a deeper understanding of inflammation's role in atherosclerosis and to decipher the devilishly intricate interactions that ignite and drive it in the arteries. These insights should enable us to make further inroads against a disease of growing worldwide importance that causes extensive disability and takes far too many lives. SA

Noninvasive tests for plaque could warn individuals destined for disaster.

MORE TO EXPLORE

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Current recommended LDL levels appear at **www.nhlbi.nih.gov/guidelines/cholesterol/**

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UNTANGLING

CAREFULLY CHOREOGRAPHED dance of chromosomes occurs during cell division. Missteps that mangle chromosomes or that send the wrong number to each daughter cell may be critical events early in the development of cancer, according to new theories.

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the roots of cancer

Recent evidence challenges long-held theories of how cells turn malignant—and suggests new ways to stop tumors before they spread

By W. Wayt Gibbs

WHAT CAUSES CANCER?

Tobacco smoke, most people would say. Probably too much alcohol, sunshine or

grilled meat; infection with cervical papillomaviruses; asbestos. All have strong links to cancer, certainly. But they cannot be root causes. Much of the population is exposed to these carcinogens, yet only a tiny minority suffers dangerous tumors as a consequence. A cause, by definition, leads invariably to its effect. The immediate cause of cancer must be some combination of insults and accidents that induces normal cells in a healthy human body to turn malignant, growing like weeds and sprouting in unnatural places.

At this level, the cause of cancer is not entirely a mystery. In fact, a decade ago many geneticists were confident that science was homing in on a final answer: cancer is the result of cumulative mutations that alter specific locations in a cell's DNA and thus change the particular proteins encoded by cancer-related genes at those spots. The mutations affect two kinds of cancer genes. The first are called tumor suppressors. They normally restrain cells' ability to divide, and mutations permanently disable the genes. The second variety, known as oncogenes, stimulate growth—in other words, cell division. Mutations lock oncogenes into an active state. Some researchers still take it as axiomatic that such growth-promoting changes to a small number of cancer genes are the initial event and root cause of every human cancer.

Others, however, including a few very prominent oncologists, are increasingly challenging that theory. No one questions that cancer is ultimately a disease of the DNA. But as biologists trace tumors to their roots, they have discovered many other abnormalities at work inside the nuclei of cells that, though not yet cancerous, are headed that way. Whole chromosomes, each containing 1,000 or more genes, are often lost or duplicated in their entirety. Pieces of chromosomes are frequently scrambled, truncated or fused together. Chemical additions to the DNA, or to the histone proteins around which it coils, somehow silence important genes—but in a reversible process quite different from mutation.

The accumulating evidence has spawned at least three hypotheses that compete with the standard dogma to explain what changes come first and which aberrations matter most in the transformation of a cell and its descendants

JEFF JOHNSON *Hybrid Medical Animation*

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from well-behaved tissue to invasive tumor. The challengers dispute the dominant view of the disease as the product of a defined genetic state. They argue that it is more useful to think of cancer as the consequence of a chaotic process, a combination of Murphy's Law and Darwin's Law: anything that can go wrong will, and in a competitive environment, the best adapted survive and prosper.

Despite that shared underlying principle, the new theories make different predictions about what kind of treatments will work best. Some suggest that many cancers could be prevented altogether by better screening, changes in diet, and new drugs—or even by old drugs, such as aspirin. Other theories cast doubt on that hope.

> "If you look at most solid tumors in adults, it looks like someone set off a bomb in the nucleus."
>
> —*William C. Hahn, Dana-Farber Cancer Institute*

Marks of Malignancy

A WORKABLE THEORY of cancer has to explain both why it is predominantly a disease of old age and why we do not all die from it. A 70-year-old is roughly 100 times as likely to be diagnosed with a malignancy as a 19-year-old is. Yet most people make it to old age without getting cancer.

Biologists estimate that more than 10 million billion cells must cooperate to keep a human being healthy over the course of an 80-year life span. If any one of those myriad cells could give rise to a tumor, why is it that less than half the population will ever contract a cancer that is serious enough to catch a doctor's attention?

One explanation is that a cell must acquire several extraordinary skills to be malignant. "Five or six different regulatory systems must be perturbed in order for a normal cell to grow as a cancer," asserts Robert A. Weinberg of the Whitehead Institute at the Massachusetts Institute of Technology. In a November 2002 review paper, he and William C. Hahn of the Dana-Farber Cancer Institute in Boston argued that all life-threatening cancers manifest at least six special abilities, or "superpowers." (Although Weinberg is one of the founding proponents of the standard paradigm, even those who challenge that theory tend to agree with this view.)

For example, cancer cells continue dividing in situations in which normal cells would quietly wait for a special chemical signal—say, from an injured neighbor. Somehow they counterfeit these progrowth messages. Conversely, tumor cells must ignore "stop dividing" commands that are sent out by the adjacent tissues they squeeze and by their own internal aging mechanisms.

All cancerous cells have serious problems of some sort with their DNA, and as they double again and again, many cells in the resulting colony end up far from the blood vessels that supply oxygen and nutrients. Such stresses trigger autodestruct mechanisms in healthy cells. Tumor cells find some way to avoid this kind of suicide. Then they have to persuade nearby blood vessels to build the infrastructure they need to thrive.

A fifth superpower that almost all cancers acquire is immortality. A culture of normal human cells stops dividing after 50 to 70 generations. That is more than enough doublings to sustain a person through even a century of healthy life. But the great majority of cells in tumors quickly die of their genetic defects, so those that survive must reproduce indefinitely if the tumor is to grow. The survivors do so in part by manipulating their telomeres, gene-free complexes of DNA and protein that protect the ends of each chromosome.

Tumors that develop these five faculties are trouble, but they are probably not deadly. It is the sixth property, the ability to invade nearby tissue and then metastasize to distant parts of the body, that gives cancer its lethal character. Local invasions can usually be removed surgically. But nine of every 10 deaths from the disease are the result of metastases.

Only an elite few cells in a tumor seem to acquire this ability to detach from the initial mass, float through the circulatory system and start a new colony in a different organ from the one that gave birth to them. Unfortunately, by the time cancers are discovered, many have already metastasized—including, in the U.S., 72 percent of lung cancers, 57

Overview/*How Cancer Arises*

- Cancer is a genetic disease. Alterations to the DNA inside cells can endow cells with morbid "superpowers," such as the ability to grow anywhere and to continue dividing indefinitely.
- Most cancer researchers have long focused on mutations to a relatively small set of cancer-related genes as the decisive events in the transformation of healthy cells to malignant tumors.
- Recently, however, other theories have emerged to challenge this view. One hypothesizes that a breakdown in DNA duplication or repair leads to many thousands of random mutations in cells. Another suggests that damage to a few "master" genes mangles the chromosomes, which then become dangerous. A third challenger proposes that abnormal numbers of chromosomes in a cell may be the first milestone on the road to cancer.

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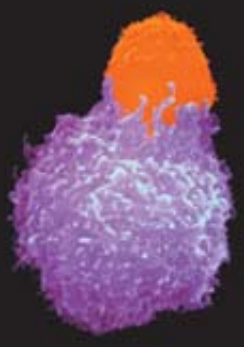
SIX DIABOLICAL SUPERPOWERS OF CANCER

1. GROWTH EVEN IN THE ABSENCE OF NORMAL "GO" SIGNALS
Most normal cells wait for an external message before dividing. Cancer cells (*image*) often counterfeit their own pro-growth messages.

2. GROWTH DESPITE "STOP" COMMANDS ISSUED BY NEIGHBORING CELLS
As the tumor (*yellow*) expands, it squeezes adjacent tissue, which sends out chemical messages that would normally bring cell division to a halt. Malignant cells ignore the commands.

3. EVASION OF BUILT-IN AUTODESTRUCT MECHANISMS
In healthy cells, genetic damage above a critical level usually activates a suicide program. Cancerous cells (*magenta*) bypass this mechanism, although agents of the immune system (*orange*) can sometimes successfully order the cancer cells to self-destruct.



4. ABILITY TO STIMULATE BLOOD VESSEL CONSTRUCTION
Tumors need oxygen and nutrients to survive. They obtain them by co-opting nearby blood vessels to form new branches (*brown streaks*) that run throughout the growing mass.

5. EFFECTIVE IMMORTALITY
Healthy cells can divide no more than 70 times. Malignant cells need more than that to make tumors. So they work around systems—such as the telomeres (*yellow*) at the end of chromosomes (*blue*)—that enforce the reproductive limit.

6. POWER TO INVADE OTHER TISSUES AND SPREAD TO OTHER ORGANS
Cancers usually become life-threatening only after they somehow disable the cellular circuitry that confines them to a specific part of the particular organ in which they arose. New growths (*orange* and *yellow*) appear and eventually interfere with vital systems.

Clockwise from top right: CHRIS JONES *Corbis;* PETER LANSDORP *University of British Columbia;* SCIENCE PHOTO LIBRARY; FRANK LYNCH *QualTek Molecular Laboratories;* ANDREJS LIEPINS/SPL; CNRI/SPL; SPL

percent of colorectal, and 34 percent of breast cancers. By then the prognosis is frequently grim.

The Order of Disorder

DOCTORS COULD CATCH incipient tumors sooner if scientists could trace the steps that cells take down the road to cancer after the initial assault to their DNA by a carcinogen or some random biochemical mishap. Researchers broadly agree on the traits of the diseased cells that emerge from the journey. It is the propelling force and the order of each milestone that are under active debate.

The dominant paradigm has been that tumors grow in spurts of mutation and expansion. Genetic damage to a cell deletes or disrupts a tumor suppressor gene—*RB*, *p53* and *APC* are among the best known—thereby suppressing proteins that normally ensure the integrity of the genome and cell division. Alternatively, a mutation may increase the activity of an oncogene—such as *BRAF*, *c-fos* or *c-erbb3*—whose proteins then stimulate the cell to reproduce.

Changes to cancer genes endow the cell with one or more superpowers, allowing it to outbreed its neighbors. The cell passes abnormalities in its DNA sequence on to its descendants, which become a kind of clone army that grows to the limits of its capacity. Eventually another random mutation to a cancer gene knocks down another obstacle, initiating another burst of growth.

Cells normally have two copies of every chromosome—one from the moth-

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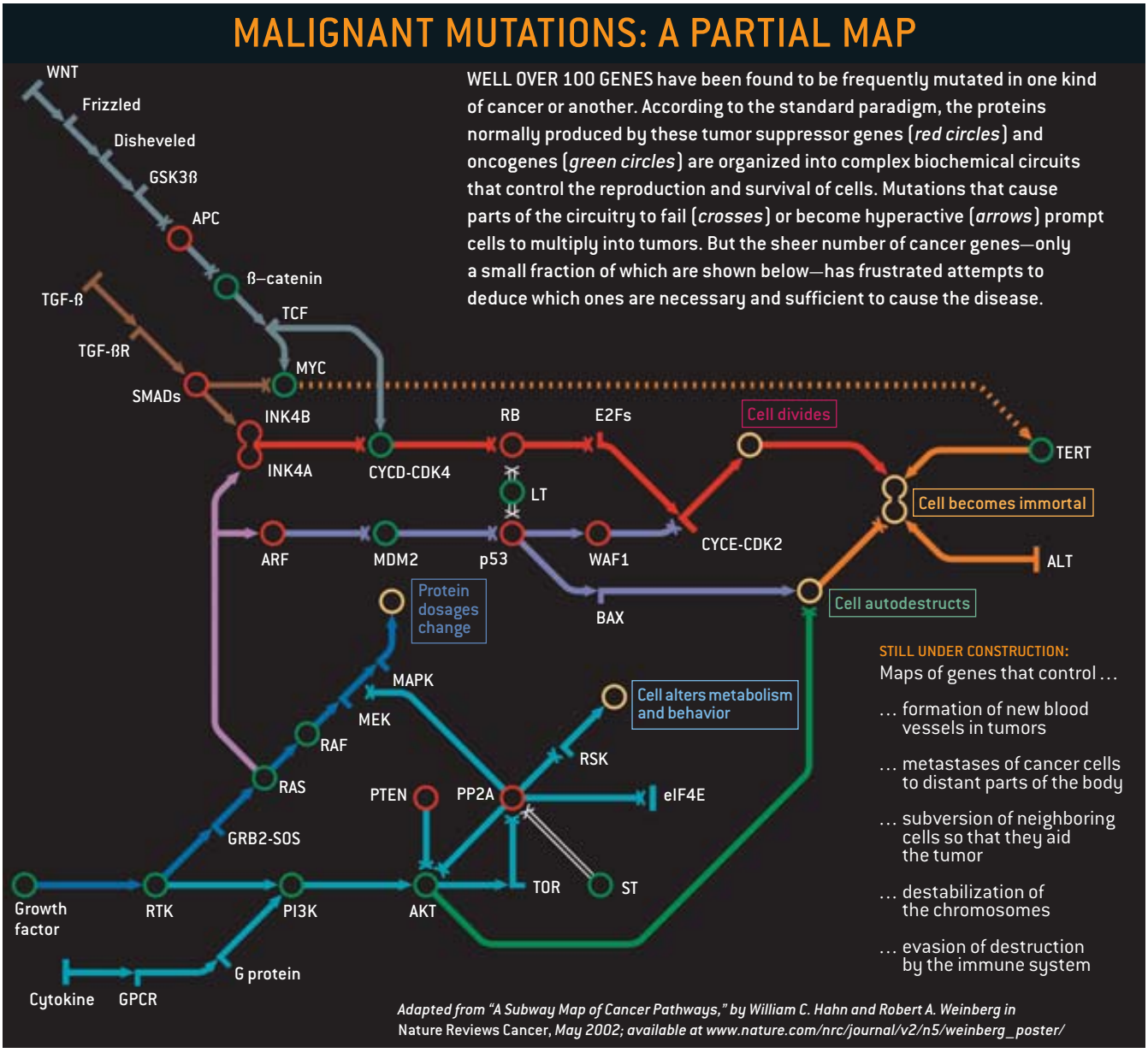
MALIGNANT MUTATIONS: A PARTIAL MAP
WELL OVER 100 GENES have been found to be frequently mutated in one kind of cancer or another. According to the standard paradigm, the proteins normally produced by these tumor suppressor genes (*red circles*) and oncogenes (*green circles*) are organized into complex biochemical circuits that control the reproduction and survival of cells. Mutations that cause parts of the circuitry to fail (*crosses*) or become hyperactive (*arrows*) prompt cells to multiply into tumors. But the sheer number of cancer genes—only a small fraction of which are shown below—has frustrated attempts to deduce which ones are necessary and sufficient to cause the disease.
WNT
Frizzled
Disheveled
GSK3ß
APC
ß–catenin
TCF
TGF-ß
TGF-ßR
SMADs
MYC
INK4B
INK4A
CYCD-CDK4
RB
E2Fs
Cell divides
TERT
LT
Cell becomes immortal
ARF
MDM2
p53
WAF1
CYCE-CDK2
ALT
Protein dosages change
BAX
Cell autodestructs
STILL UNDER CONSTRUCTION:
Maps of genes that control . . .
. . . formation of new blood vessels in tumors
. . . metastases of cancer cells to distant parts of the body
. . . subversion of neighboring cells so that they aid the tumor
. . . destabilization of the chromosomes
. . . evasion of destruction by the immune system
MAPK
MEK
RAF
RAS
Cell alters metabolism and behavior
RSK
PTEN
PP2A
eIF4E
GRB2-SOS
TOR
ST
Growth factor
RTK
PI3K
AKT
G protein
Cytokine
GPCR
Adapted from "A Subway Map of Cancer Pathways," by William C. Hahn and Robert A. Weinberg in Nature Reviews Cancer, May 2002; available at www.nature.com/nrc/journal/v2/n5/weinberg_poster/

er, the other from the father—and thus two copies, or alleles, of every gene. (In males, the single X and Y chromosomes are notable exceptions.) A mutation to just one allele is enough to activate an oncogene permanently. But it takes two hits to knock out both alleles of a tumor suppressor gene. Four to 10 mutations in the right genes can transform any cell. Or so the theory goes.

The mutant-gene paradigm gained almost universal acceptance because it explained very well what scientists saw in their experiments on genetically engineered mice and human cell cultures. But new technologies now allow researchers to study the genomes of cancerous and precancerous cells taken directly from people. Many recent observations seem to contradict the idea that mutations to a few specific genes lie at the root of all cancers.

Unexplained Phenomena

IN APRIL 2003, for example, Muhammad Al-Hajj of the University of Michigan at Ann Arbor and his colleagues reported that they had identified distinguishing marks for a rare subset of cells within human breast cancers that can form new tumors. As few as 100 cells of this type quickly spawned disease when injected into mice lacking an immune system. Tens of thousands of other cells, harvested from the same nine breast malignancies but lacking the telltale marks, failed to do so. "This is the first tumor-initiating cell anyone has isolated for solid tumors," says John E. Dick, a biologist at the University of Toronto who has identified similar cells for leukemia.

The tantalizing implication, Dick explains, is that just a small fraction of the cells in a tumor are responsible for its growth and metastasis. If that is shown to be true for humans as well as mice, it could pose a problem for the mutant-gene theory of cancer. If mutations, which are copied from a cell to its progeny, give tumor cells their powers, then shouldn't all clones in the army be equally powerful?

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In fact, most tumors are not masses of identical clones. On the contrary, closer examination has revealed amazing genetic diversity among their cells, some of which are so different from normal human cells (and from one another) that they might fairly be called new species.

A few cancer-related genes, such as *p53,* do seem to be mutated in the majority of tumors. But many other cancer genes are changed in only a small fraction of cancer types, a minority of patients, or a sprinkling of cells within a tumor. David Sidransky of the Johns Hopkins University School of Medicine and his co-workers tested DNA from 476 tumors of various kinds. They reported in April 2003 that the oncogene *BRAF* was altered in two thirds of papillary thyroid cancers but not in any of several other kinds of thyroid cancers.

Moreover, some of the most commonly altered cancer genes have oddly inconsistent effects. Bert E. Vogelstein's group at Johns Hopkins found that the much studied oncogenes *c-fos* and *c-erbb3* are curiously less active in tumors than they are in nearby normal tissues. The tumor suppressor gene *RB* was recently shown to be hyperactive—not disabled—in some colon cancers, and, perversely, it appears to protect those tumors from their autodestruct mechanisms.

The "two hit" hypothesis—that both alleles of a tumor suppressor gene must be deactivated—has also been upended by the discovery of a phenomenon called haploinsufficiency. In some cancers, tumor suppressors are not mutated at all. Their output is simply reduced, and that seems to be enough to push cells toward malignancy. This effect has now been seen for more than a dozen tumor suppressor genes. Searching for the mere presence or absence of a gene's protein is too simplistic. Dosage matters.

Beyond Mutation

RESEARCHERS ARE NOW looking more closely at other phenomena that could dramatically alter the dosage of a protein in a cell. Candidates include the loss or gain of a chromosome (or part of one) containing the gene; changes in the concentration of other proteins that regulate how the gene is transcribed from DNA to RNA and translated into a protein; even so-called epigenetic phenomena that alter gene activity by reversible means. All these changes are nearly ubiquitous in established cancers.

"If you look at most solid tumors in adults, it looks like someone set off a bomb in the nucleus," Hahn says. "In most cells, there are big pieces of chromosomes hooked together and duplications or losses of whole chromosomes."

Scientists have yet to settle on a term for the suite of chromosomal aberrations seen in cancer. The word "aneuploidy" once referred to an abnormal number of chromosomes. But more recently, it has been used in a broader sense that encompasses chromosomes with truncations, extensions or swapped segments.

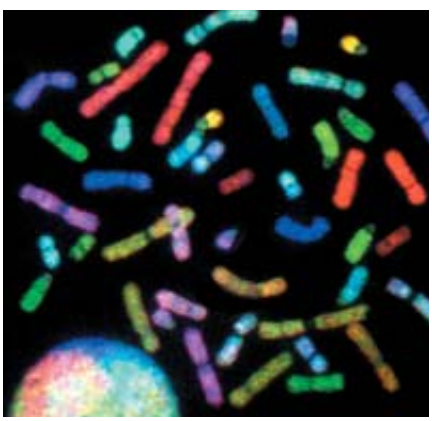
Almost a century ago German biologist Theodor Boveri noticed the strange imbalance in cancer cells between the numbers of maternal versus paternal chromosomes. He even suggested that aneuploid cells might cause the disease. But scientists could find no recurrent pattern to the chromosomal chaos—indeed, the genome of a typical cancer cell is not merely aneuploid but is unstable as well, changing every few generations. So Boveri's idea was dropped as the search for oncogenes started to bear fruit. The aneuploidy and massive genomic instability inside tumor cells were dismissed as side effects of cancer, not prerequisites.

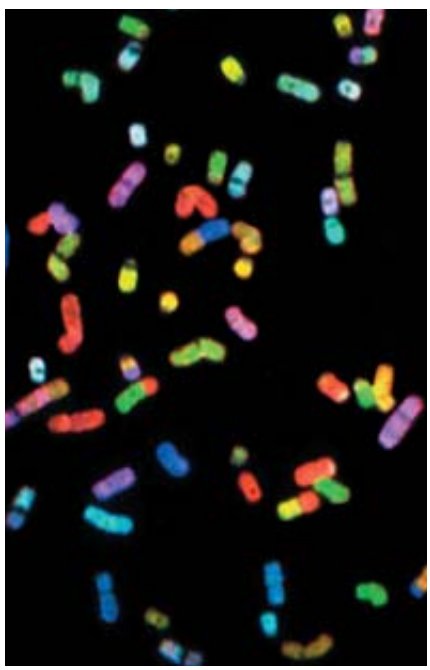
But the oncogene/tumor suppressor gene hypothesis has also failed, despite two decades of effort, to identify a particular set of gene mutations that occurs in every instance of any of the most common and deadly kinds of human cancer. The list of cancer-related mutations has grown to more than 100 oncogenes and 15 tumor suppressor genes. "The rate at which these molecular markers are being identified continues to increase rapidly," lamented Weinberg and Hahn in their 2002 review. "As a consequence," they added, "it remains possible that each tumor is unique" in the pattern of its genetic disarray.

Hahn reflected on this possibility in his Boston office in January 2003. Along with Weinberg, he has pioneered the construction of artificial tumors using mutant cancer genes. But he acknowledged that they cannot be the whole story. "The question is which comes first," he said. "Mutations or aneuploidy?"

There are at least three competing answers. Let us call them the modified dogma, the early instability theory and the all-aneuploidy theory. Encouragingly, the theories seem to be converging as

ABERRANT CHROMOSOMES IN A CANCER CELL can alter the dosage of thousands of genes at once. A healthy cell (*below*) contains one pair of each of the 22 kinds of chromosomes (*distinct colors*), plus two sex chromosomes. In a malignant cell (*right*), some chromosomes contain arms of different types (*multicolored, at left edge*). Others are missing limbs (*royal blue*) or are present in the wrong number (*lime green*).





HESED M. PADILLA-NASH AND THOMAS REID *National Cancer Institute*

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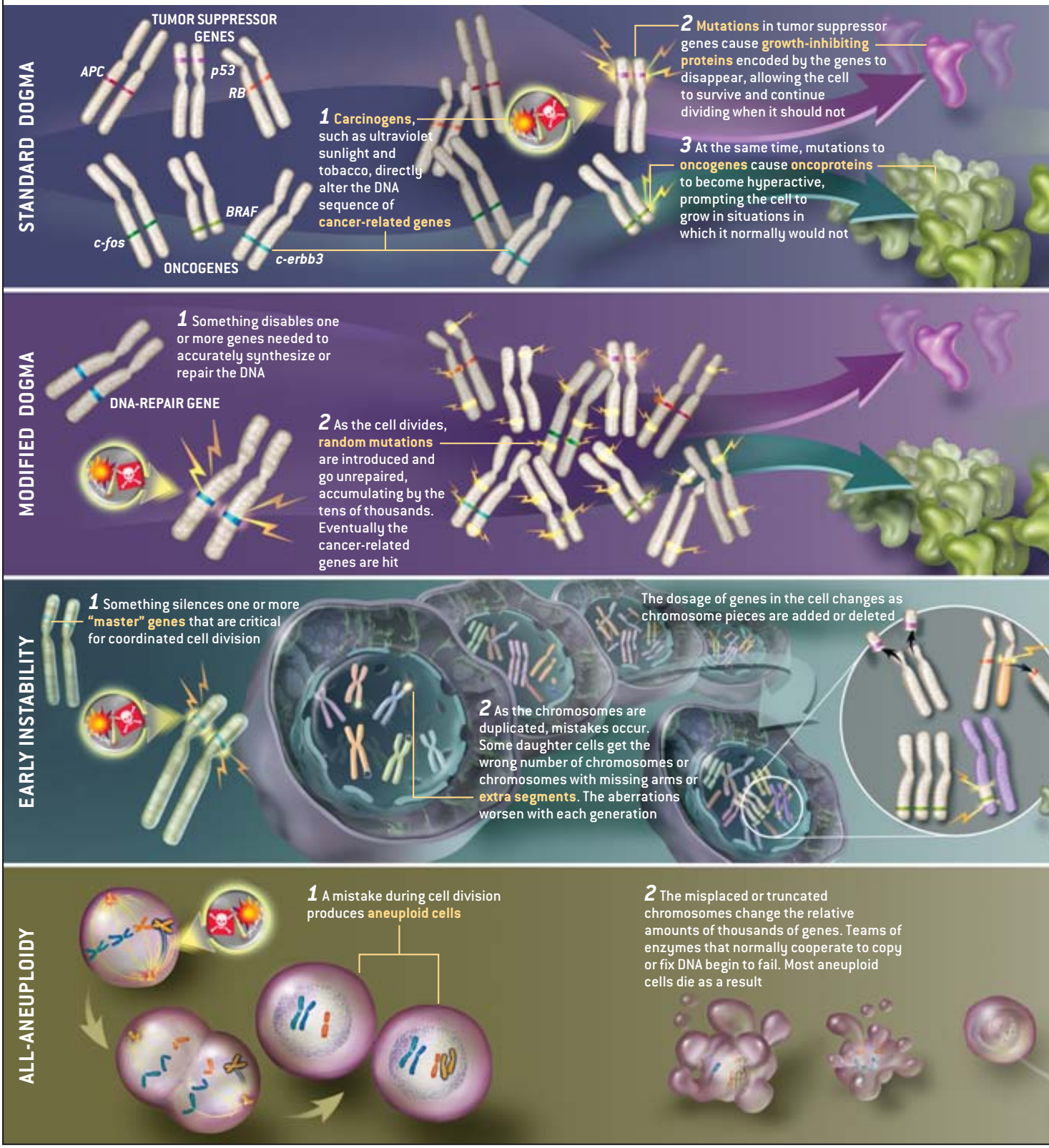
THE GENESIS OF CANCER: FOUR THEORIES

FOR DECADES, the most widely accepted view of how cancer begins has been that mutations to a handful of special genes eliminate tumor suppressor proteins and activate oncoproteins. More recently, three alternative theories have gained currency. One modifies the standard paradigm by postulating a dramatic increase in the accumulation of random mutations throughout the genomes of precancerous cells. Two other theories focus on the role of aneuploidy—


STANDARD DOGMA
TUMOR SUPPRESSOR GENES
APC
p53
RB
BRAF
c-fos
c-erbb3
ONCOGENES
1 Carcinogens, such as ultraviolet sunlight and tobacco, directly alter the DNA sequence of cancer-related genes
2 Mutations in tumor suppressor genes cause growth-inhibiting proteins encoded by the genes to disappear, allowing the cell to survive and continue dividing when it should not
3 At the same time, mutations to oncogenes cause oncoproteins to become hyperactive, prompting the cell to grow in situations in which it normally would not
MODIFIED DOGMA
1 Something disables one or more genes needed to accurately synthesize or repair the DNA
DNA-REPAIR GENE
2 As the cell divides, random mutations are introduced and go unrepaired, accumulating by the tens of thousands. Eventually the cancer-related genes are hit
EARLY INSTABILITY
1 Something silences one or more "master" genes that are critical for coordinated cell division
2 As the chromosomes are duplicated, mistakes occur. Some daughter cells get the wrong number of chromosomes or chromosomes with missing arms or extra segments. The aberrations worsen with each generation
The dosage of genes in the cell changes as chromosome pieces are added or deleted
ALL-ANEUPLOIDY
1 A mistake during cell division produces aneuploid cells
2 The misplaced or truncated chromosomes change the relative amounts of thousands of genes. Teams of enzymes that normally cooperate to copy or fix DNA begin to fail. Most aneuploid cells die as a result

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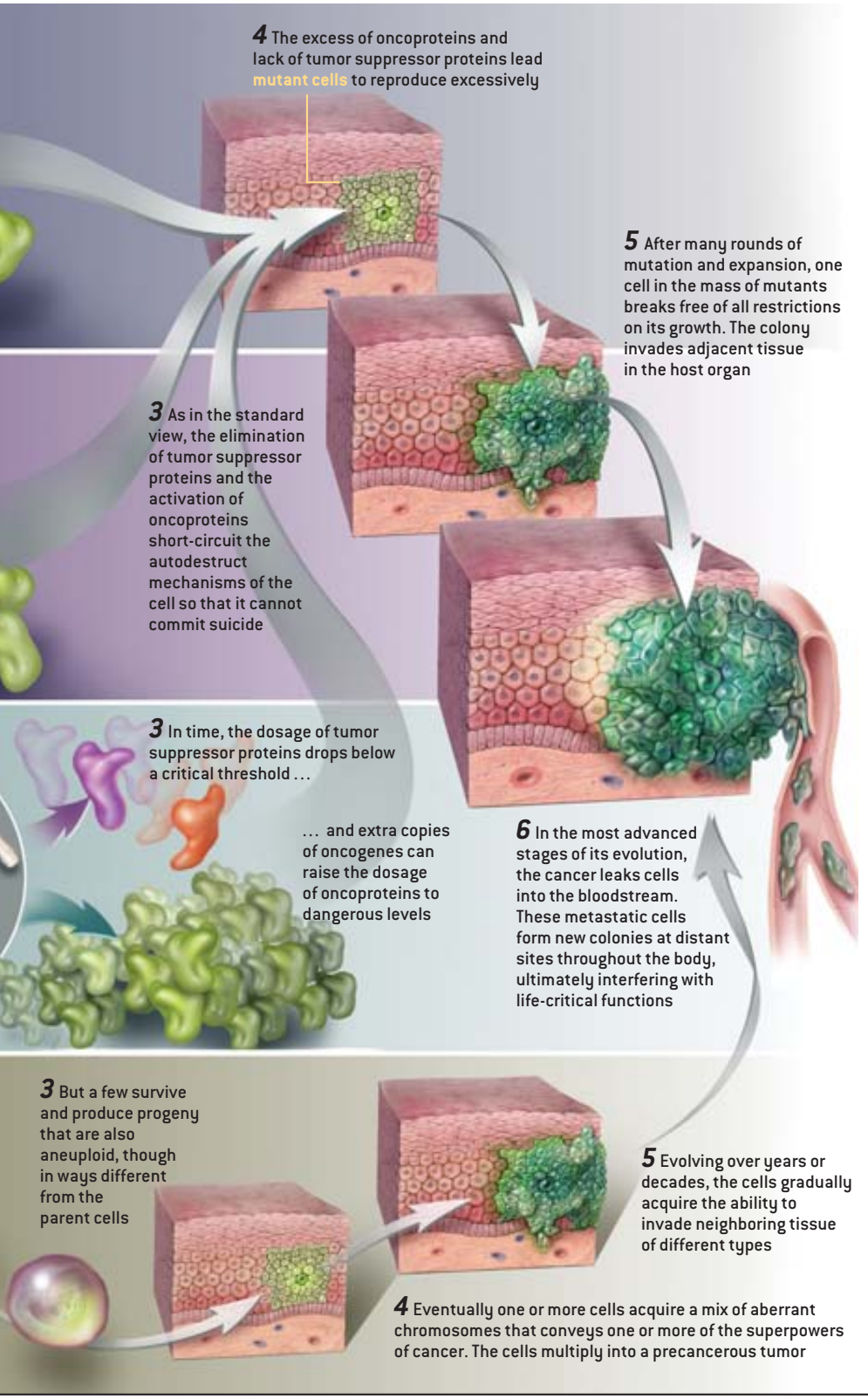
large-scale aberrations in the chromosomes. Aneuploidy could lead to genomic instability early on and later mutate known cancer genes. Or it may form tumors through an almost infinite variety of genetic changes.


4 The excess of oncoproteins and lack of tumor suppressor proteins lead mutant cells to reproduce excessively
5 After many rounds of mutation and expansion, one cell in the mass of mutants breaks free of all restrictions on its growth. The colony invades adjacent tissue in the host organ
3 As in the standard view, the elimination of tumor suppressor proteins and the activation of oncoproteins short-circuit the autodestruct mechanisms of the cell so that it cannot commit suicide
3 In time, the dosage of tumor suppressor proteins drops below a critical threshold . . .
. . . and extra copies of oncogenes can raise the dosage of oncoproteins to dangerous levels
6 In the most advanced stages of its evolution, the cancer leaks cells into the bloodstream. These metastatic cells form new colonies at distant sites throughout the body, ultimately interfering with life-critical functions
3 But a few survive and produce progeny that are also aneuploid, though in ways different from the parent cells
5 Evolving over years or decades, the cells gradually acquire the ability to invade neighboring tissue of different types
4 Eventually one or more cells acquire a mix of aberrant chromosomes that conveys one or more of the superpowers of cancer. The cells multiply into a precancerous tumor

CHRISTY KRAMES

they bend to accommodate new experimental results.

The modified form of the standard dogma revives an idea proposed in 1974 by Lawrence A. Loeb, now at the University of Washington. He and others have estimated that random mutation will affect just one gene in any given cell over a lifetime. Something—a carcinogen, reactive oxidants, or perhaps a malfunction in the cell's DNA duplication and repair machinery—must dramatically accelerate the mutation rate, Loeb argues. "I think that is probably right," Hahn concurs. Otherwise, he says, "cells wouldn't accumulate a sufficient number of mutations to form a tumor."

Loeb believes that "early during the genesis of cancer there are enormous numbers of random mutations—10,000 to 100,000 per cell." Evidence for the theory is still slim, he acknowledges. Counting random mutations is hard; scientists must compare the genomes of individual cells letter by letter. Advances in biotechnology have only recently made that feasible.

The modified dogma thus adds a prologue to the accepted life history of cancer. But the most important factors are still mutations to genes that serve to increase the reproductive success of cells. Mangled and ever changing chromosomes are but fortuitous by-products.

Unstable from the Outset

CRISTOPH LENGAUER and Vogelstein of Johns Hopkins, both well-known colon cancer specialists, have proposed an alternative theory in which chromosomal instability can occur early on. The genetic flux then combines forces with natural selection to produce a benign growth that may later be converted to an invasive malignancy and life-threatening metastases.

In their hypothesis, there are several "master" genes whose function is critical for a cell to reproduce correctly. If as few as one of these genes is disabled, either by mutation or epigenetically, the cell stumbles each time it attempts cell division, muddling some of the chromosomes into an aneuploid state. One result is to increase 100,000-fold the rate at which

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cells randomly lose one of the two alleles of their genes. For a tumor suppressor gene, a lost allele may effectively put the gene out of commission, either because the remaining copy is already mutated or because of the haploinsufficiency effect. Lengauer and Vogelstein still assume that some cancer genes must be altered before a malignancy can erupt.

In December 2002, together with Martin A. Nowak and Natalia L. Komarova of the Institute for Advanced Study in Princeton, N.J., Lengauer and Vogelstein published a mathematical analysis that applied this theory to nonhereditary colon cancer. Even if there are as few as half a dozen master genes in the human genome, they calculated, it is very likely that a master gene will be disabled before a particular cancer gene is hit.

Calculations are fine, but only empirical evidence is persuasive. Some recent studies do support the early instability theory. In 2000 Lengauer's laboratory examined colon adenomas—benign polyps that occasionally turn malignant—and observed that more than 90 percent had extra or missing pieces of at least one chromosome. More than half had lost the long arm of chromosome 5, home to the *APC* tumor suppressor gene, long implicated in the formation of colon cancer. Other researchers have discovered similarly aberrant chromosomes in precancerous growths taken from the stomach, esophagus and breast.

The early instability theory still has some loose ends, however. How can cells with shifty chromosomes outcompete their stable counterparts? Under normal conditions, they probably do not, suggests immunologist Jarle Breivik of the University of Oslo. But in a "war zone," where a carcinogen or other stressor is continually inflicting damage to cells, normal cells stop dividing until they have completed repairs to their DNA. Genetically unstable cells get that way because their DNA repair systems are already broken. So they simply ignore the damage, keep on proliferating, and thus pull ahead, Breivik hypothesizes.

He cites an experiment in which Lengauer and his colleagues exposed human cell lines to toxic levels of a carcinogen in broiled meat. Only a few cells developed resistance and survived. All were genetically unstable before exposure to the toxin.

But what jumbles the chromosomes in the first place? No genes have yet been conclusively identified as master genes, although several strong suspects have surfaced. German A. Pihan of the University of Massachusetts Medical School and his co-workers may have uncovered a clue in a March 2003 study of 116 premalignant tumors caught before they had invaded neighboring tissues of the cervix, prostate and breast. Thirty to 72 percent of the growths contained defective centrosomes, structures that appear during cell division to help separate the duplicated chromosomes from the originals. Most of those cells were aneuploid. Scientists are still working out the genes that control centrosome formation and function; any of them might be a master gene.

Aneuploidy All the Way Down

ON THE OTHER HAND, maybe cells can become malignant even before any master genes, oncogenes or tumor suppressor genes are mutated. Peter H. Duesberg and Ruhong Li of the University of California at Berkeley have put forth a third theory: nearly all cancer cells are aneuploid because they start that way. Lots of things can interfere with a dividing cell so that one of its daughter cells is cheated of its normal complement of 46 chromosomes and the other daughter is endowed with a bonus. Asbestos fibers, Duesberg notes, can physically disrupt the process.

Most aneuploid cells are stillborn or growth-retarded. But in the rare survivor, he suggests, the dosage of thousands of genes is altered. That corrupts teams of enzymes that synthesize and maintain DNA. Breaks appear in the double helix, destabilizing the genome further. "The more aneuploid the cell is, the more unstable it is, and the more likely it will produce new combinations of chromosomes that will allow it to grow anywhere," Duesberg explains.

Unlike the three other theories, the all-aneuploidy hypothesis predicts that the emergence and progress of a tumor are more closely connected to the assortment of chromosomes in its cells than to the mutations in the genes on those chromosomes. Some observations do seem to corroborate the idea.

In May 2003, for instance, Duesberg and scientists at the University of Heidelberg reported on experiments with normal and aneuploid hamster embryos. The more the cells deviated from the correct number of chromosomes, the faster aberrations accumulated in their chromosomes. Genomic instability rose exponentially with greater aneuploidy.

Thomas Ried, chief of cancer genomics at the National Cancer Institute, has obtained supporting evidence in humans with cervical and colorectal cancers. "Unequivocally, there are recurrent patterns of genomic imbalances," Ried avers. "Every single case of [nonhereditary] colorectal cancer, for example, has gains of chromosomes 7, 8, 13 or 20 or a loss of 18. In cervical cancer, aneuploidy of chromosome 3 happens very early, and those cells seem to have a selective advantage." Ried finds the average number of abnormal chromosomes increasing gradually from 0.2 in a normal cell to 12 in the cells of metastatic colon tumors.

BRANCHING POINTS IN

1914 Theodor Boveri suggests that aberrant chromosomes may cause cancer

1927 Hermann J. Muller observes that radiation mutates cells

1951 Muller proposes theory that multiple mutations turn a cell malignant

1915 1920 1925 1930 1935

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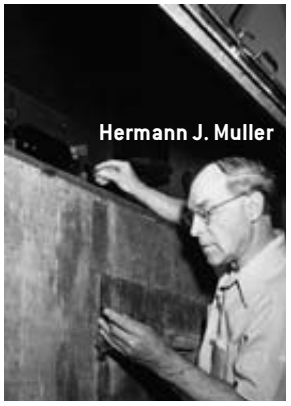
THE EVOLUTION OF CANCER THEORY



1971 Alfred G. Knudson explains different rates of inherited and spontaneous retinal cancer with the hypothesis that two "hits," or damaging mutations, are needed to disable both alleles of the *RB* gene and that one mutation can be inherited

1997 Christoph Lengauer and Vogelstein demonstrate dramatic increase in gain and loss of chromosomes in colon tumor cells and propose that chromosomal instability is a critical early event that leads to the mutation of oncogenes and tumor suppressor genes

2002 Thomas Ried identifies recurrent patterns of aneuploidy in cervical and colon cancers

2003 The number of identified cancer genes, now well over 100, continues to grow rapidly

1999 Peter Duesberg publishes detailed theory of how aneuploidy may be sufficient to cause cancer itself, even without mutations to any particular set of genes

1990 Bert Vogelstein and Eric R. Fearon publish a model of sequential gene mutations that lead to colon cancer

1986 Robert Weinberg isolates *RB*, the first tumor suppressor gene

1974 Lawrence Loeb argues that random mutations must accumulate fast in cells that become malignant

1960 Discovery that an exchange of DNA between chromosomes 9 and 22 leads to chronic myelogenous leukemia

1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000

"So I think Duesberg is right that aneuploidy can be the first genetic aberration in cancer cells," Ried says. "But he also argues that no gene mutations are required. This is simply not true."

Stopping Cancer at Its Roots

NEITHER THE standard dogma nor any of the new theories can explain the 100-odd diseases we call cancer as variations of a single principle. And all the theories will need to be expanded to incorporate the role of epigenetic phenomena.

It is important to determine which of the ideas is more correct than the others, because they each make different predictions about the kinds of therapy that will succeed. In the standard view, tumors are in effect addicted to the proteins produced by oncogenes and are poisoned by tumor suppressor proteins. Medicines should therefore be designed to break the addiction or supply the poison. Indeed, this strategy is exploited by some newer drugs, such as Gleevec (for rare forms of leukemia and stomach cancer) and Herceptin (for one variety of advanced breast cancer).

But all existing therapies fail in some patients because their tumors evolve into a resistant strain. Loeb fears that there may be no easy way around that problem. "If I am right, then within any given tumor, which contains roughly 100 million cells, there will be cells with random mutations that protect them from any treatment you can conceive," Loeb says. "So the best you can hope for is to delay the tumor's growth. You are not going to cure it."

For the elderly—who, after all, are the main victims of cancer—a sufficient delay may be as good as a cure. And even better than slowing the growth of a tumor would be to delay its formation in the first place. If Lengauer and other adherents of the early instability theory succeed in identifying master genes, then it should also be possible to make drugs that protect or restore their function. Lengauer says his group has already licensed cell lines to the pharmaceutical industry to use in drug screening.

Screening of a different kind may be the best approach if the all-aneuploidy theory is correct. There is no known means of selectively killing cells with abnormal chromosomes. But a biopsy that turns up a surfeit of aneuploid cells might warrant careful monitoring or even preventive surgery in certain cases. And Duesberg suggests that foods, drugs and chemicals should be tested to identify compounds that cause aneuploidy.

One day science will produce a definitive answer to the question of what causes cancer. It will probably be a very complicated answer, and it may force us to shift our hope from drugs that cure the disease to medicines that prevent it. Even without a clear understanding of why, doctors have discovered that a daily baby aspirin seems to prevent colon adenomas in some adults. The effect is small. But it is a step from chemotherapy toward a better alternative: chemoprevention. SA

W. Wayt Gibbs is senior writer for Scientific American.

MORE TO EXPLORE

Chromosome Segregation and Cancer: Cutting through the Mystery. Prasad V. Jallepalli and Cristoph Lengauer in *Nature Reviews Cancer,* Vol. 1, No. 2, pages 109–117; November 2001.

Rules for Making Human Tumor Cells. William C. Hahn and Robert A. Weinberg in *New England Journal of Medicine,* Vol. 347, No. 20, pages 1593–1603; November 14, 2002.

Multiple Mutations and Cancer. Lawrence A. Loeb, Keith R. Loeb and Jon P. Anderson in *Proceedings of the National Academy of Sciences USA,* Vol. 100, No. 3, pages 776–781; February 4, 2003.

From left to right: SPL (*Boveri*); HULTON-DEUTSCH COLLECTION/CORBIS (*Muller*); ALEX WONG Getty Images (*Vogelstein*); MARC GELLER (*Duesberg*)

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The bone decay of osteoporosis can cripple, but an improved understanding of how the body builds and loses bone is leading to ever better prevention and treatment options

RESTORING AGING BONES

By Clifford J. Rosen

NEW TREATMENTS and preventives for osteoporosis are allowing women—and men—to avoid its worst consequences.

Late in 2002 a new patient, 72-year-old Maxine LaLiberte, limped into my office. She said she had always been very active. She baby-sat frequently for her nine grandchildren and had been looking forward to a long-planned cross-country motor home trip with her husband. But now the excruciating pain between her shoulder blades was curtailing her movements and making her feel old.

I was all too familiar with those symptoms in people my patient's age. Even without examining her, I was reasonably sure that one or more of her vertebrae had fractured as a result of osteoporosis, a disorder characterized by bone loss so severe that fractures occur spontaneously or from even minor bumps.

Osteoporosis afflicts about 10 million Americans, especially women past menopause. Fully half of all postmenopausal women will incur an osteoporosis-related fracture during their lives. Fortunately, the outlook for people with osteoporosis has never been better. Drugs are now available that can restore lost bone and thereby greatly reduce the risk of additional breaks. Furthermore, recent insights into the cellular and molecular bases of osteoporosis have generated exciting ideas for new and even more effective therapies.

Just a decade ago therapeutic options for osteoporosis consisted mainly of calcium supplements, painkillers and, for women past menopause, estrogen replacement therapy—helpful treatments, but imperfect. Estrogen replacement therapy, for instance, increases the risk for heart attack, stroke, breast cancer and blood clots. Today, in contrast,

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OSTEOPOROTIC SPINE (*left*) shows the bone thinning and collapsed vertebrae that are characteristic of the disease. In contrast, the vertebrae of a normal spine (*right*) are dense and uniform.

pharmacies stock several drugs that reduce the likelihood of new fractures by as much as 70 percent in the first year of treatment.

Similarly dramatic improvements have taken place in diagnosis. Not long ago a fracture was often the only tip-off that someone had osteoporosis. But physicians are now using a sophisticated in-office tool called dual-energy x-ray absorptiometry (DEXA) to measure bone mineral density at sites especially susceptible to fracture. DEXA is allowing doctors to diagnose osteoporosis much earlier—in time to initiate drug treatment that can keep bones intact and prevent fractures from occurring. In addition, DEXA can be a useful screening tool to predict the likelihood of future breaks at any site [*see box on opposite page*].

Recent research has also yielded a new appreciation for heredity's role in osteoporosis. The disorder was long considered a "traumatic" condition, in which decades of skeletal wear and tear culminate in fractures and pain. Genetic investigations have now revealed, however, that genes influence bone density and, hence, the risk of fractures. These studies indicate that genetic differences account for up to 70 percent of human variability in bone mass, although such factors as diet and exercise play a part, too. Apparently, many different genes influence propensity. As specific osteoporosis-promoting gene variants are found, they could form the basis for tests to detect susceptibility and could also lead to drugs able to counteract their effects.

Reversing Silent Thievery

THE NEED FOR better preventive and therapeutic options is urgent. Osteoporosis, which literally means "porous bones," is the underlying cause of virtually all broken bones in people older than 65. The vertebrae, hips and wrists are particularly susceptible to osteoporotic fractures. These broken bones can cause chronic, disabling pain and—in the case of the hip—often usher in a series of events that can lead to death: of the 275,000 older Americans who suffer a broken hip every year, 20 percent die within a year of the episode from blood clots, infections or undernutrition. In addition to the 10 million Americans with existing osteoporosis, another 18 million have low bone mass (osteopenia), a condition that does not qualify as osteoporosis but heightens their risk for eventually developing the disorder.

Medicines introduced in the past 10 years are designed to alleviate the suffering of osteoporosis by interfering with a process known as bone remodeling, or turnover. Seemingly inert when viewed from the outside, bone is a living tissue that ceaselessly destroys and rebuilds itself throughout adult life. This remodeling essentially replaces the entire skeleton every 10 years—dissolving, or resorbing, old bone and completely replacing it with new. Remodeling undoubtedly serves some useful functions, such as freeing calcium from bone for use by various tissues and repairing microfractures. But defective remodeling underlies the development of osteoporosis.

During childhood and adolescence, bone formation proceeds faster than resorption, causing bone density to increase until young adults attain their peak bone mass at around age 18. Density stays constant throughout young adulthood as bone formation and resorption proceed at the same rate. But around age 40, everyone begins to experience some bone thinning as resorption begins to outpace bone formation. For several reasons, however, the risk of osteoporosis is much greater in women, who account for 80 percent of cases.

The average woman attains a peak bone mass that is generally about 5 percent below that of a man's, so women have a bit less bone density "in the bank" when age-related bone loss begins. In ad-

Overview/*Osteoporosis*

- Bones are constantly being dissolved and remade throughout life. Osteoporosis results when bone-degrading cells, called osteoclasts, are more active than bone-building cells, called osteoblasts.
- Novel treatments for osteoporosis depend on blocking the activity of osteoclasts or killing them.

ILLUSTRATION BY MELISSA SZALKOWSKI, GCa *Photo Researchers, Inc.* (*left spine*), CORBIS (*right spine*) (*preceding pages*); ROBERT M. LEVIN *Boston Medical Center* (*this page*)

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dition, women lose an important bone protector—estrogen—at menopause. As a result, bone loss in women can increase sharply for some four to seven years after the shutoff of estrogen at menopause.

Two types of bone cells carry out remodeling—bone-forming osteoblasts and large, bone-resorbing osteoclasts [*see box on next page*]. Both cell types come together in three million to four million sites, termed basic multicellular units of bone remodeling, that are scattered throughout the skeleton. Remodeling always occurs in the same sequence: a rapid (two- to three-week) bone resorption phase followed by a slower (two- to three-month) bone formation phase.

Resorption begins when the osteoclasts attach to bone surfaces and release substances that degrade the structural parts of bone—calcium, other minerals and the protein collagen. This degrading activity forms an indentation called a resorption pit, after which the osteoclasts disappear, probably as a consequence of programmed cell death (also called apoptosis, or cell suicide). Remodeling's bone formation phase begins when osteoblasts—perhaps attracted by growth factors released during bone resorption—converge on the resorption pit, filling it with new bone by synthesizing and secreting collagen and other proteins. Calcium, phosphorus and other minerals then crystallize around the collagen matrix to form hydroxyapatite, the hard, mineralized part of bone that accounts for 90 percent of its mass.

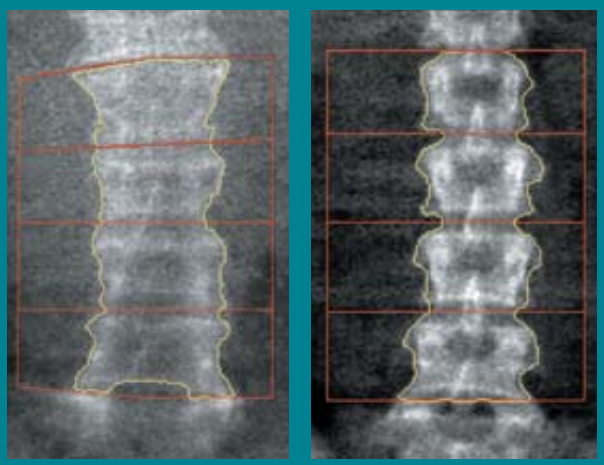
Until 2002, all drugs approved for treating osteoporosis were considered antiresorptives, because they slow resorption more than they promote formation (although anything that affects one process also affects the other to some degree). Drugs of one antiresorptive class in particular—the bisphosphonates—have transformed osteoporosis treatment over the past decade and are now the first choice for both men and women. These oral agents slow bone remodeling by attaching readily to the mineral part of bone, where they wait for osteoclasts to bind to the bone's surface. Once that happens, the bisphosphonates diffuse into the osteoclasts and induce those cells to self-destruct.

Large-scale, randomized clinical trials have shown unequivocally that the most potent bisphosphonates—alendronate (Fosamax) and risedronate (Actonel)—not only prevent further bone loss but can also increase bone density in most patients by 5 to 10 percent over three years. That bone buildup may seem modest, but it is enough to reduce the risk of spine, hip and wrist fractures by as much as 50 percent at three years, with more significant fracture reduction evident in the first year of therapy. The bisphosphonates need to be taken just once a week and seem exceptionally safe: aside from heartburn, side effects are rare. These drugs have been in use for only a decade, however, so their long-term safety beyond 10 years remains to be demonstrated.

Seeking New Drug Targets

MOTIVATED IN PART by a desire for more effective osteoporosis drugs, scientists are now intensively studying how bone remodeling is regulated so that

TO SCREEN OR NOT TO SCREEN?



SPINAL SCANS made with dual-energy x-ray absorptiometry (DEXA) are used to diagnose osteoporosis. Bone in the lumbar (lower) spine of someone with osteoporosis (*left*) is much less dense than that in the spine of a healthy individual (*right*). The vertebrae have also begun to collapse, shifting the spine out of alignment (*indicated by red lines*).

SHOULD OLDER WOMEN be screened to see if they are at risk for osteoporotic fractures? Ever since tools for measuring bone mineral density became available to doctors, this question has elicited intense controversy.

Studies show that density measurements—of the hip or spine, for example—can reliably predict a person's risk for a fracture at that site. The "gold standard" for measuring bone mineral density is a technology called dual-energy x-ray absorptiometry (DEXA), which uses x-rays but involves very little radiation exposure. DEXA diagnoses osteoporosis when it finds that the measure of density is much lower than the average for healthy young women at the spine, hip or wrist (2.5 or more standard deviations from the mean).

DEXA not only tells a woman whether she has osteoporosis; it can predict her risk for fracture at that site over the next several years—potentially useful knowledge, because new drugs can rebuild bone density and prevent fractures before they occur. Yet critics of screening note that mineral density is just one of many factors (including exercise, nutrition, genetics and bone quality) that influence a woman's fracture risk. In addition, critics say, women worried about low scores might be scared into taking drugs, such as estrogen, that could have dangerous side effects.

In September 2002 the U.S. Preventive Services Task Force came down firmly on the side of screening, recommending for the first time that all women aged 65 and older have their bone density measured at least once to assess their risk of fracture. In support of its recommendation, the task force emphasized that the risk for osteoporosis "increases steadily and substantially with age." Compared with women aged 50 to 54, the task force wrote, the odds of having osteoporosis are 5.9 times as high in women aged 65 to 69 and 14.3-fold as high in women aged 75 to 79. —*C.J.R.*

FAYE LIQUE *Maine Center for Osteoporosis Research and Education*

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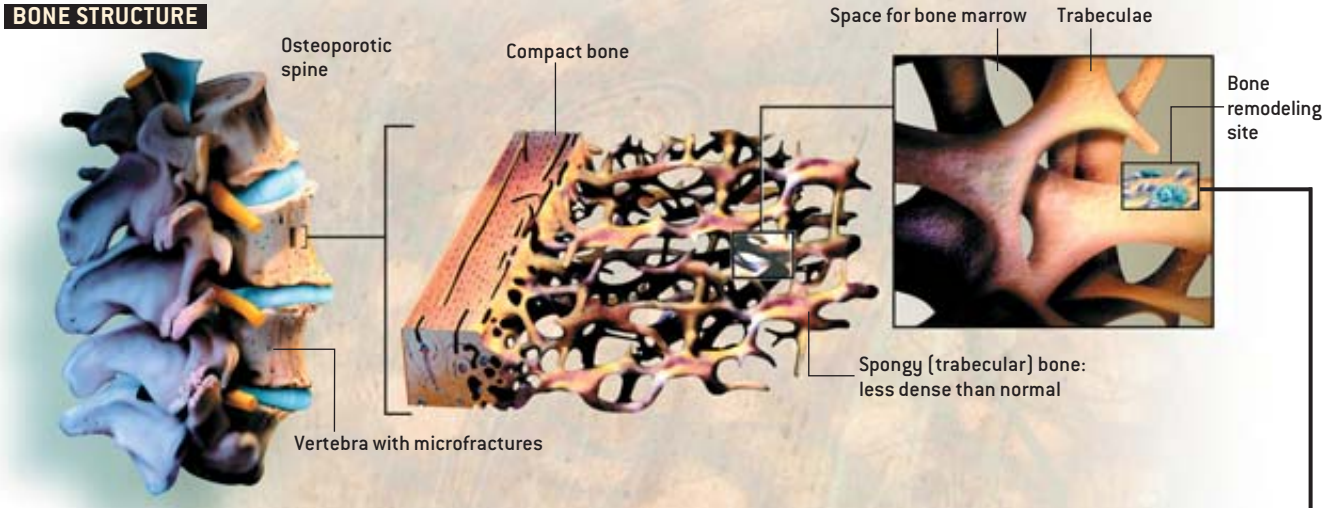
OSTEOPOROSIS AND TARGETS FOR THERAPY

THE BODY CONTINUOUSLY renews, or remodels, the bones throughout life using two types of cells: osteoclasts, which destroy old bone, and osteoblasts, which make new bone. Osteoporosis results when the normal balance between the activity of osteoclasts and osteoblasts becomes disrupted, tipping the scales in favor of bone destruction. Various drugs are now on the market or under development (*gold boxes*) to treat osteoporosis by decreasing the action of osteoclasts or boosting that of osteoblasts.

BONE STRUCTURE

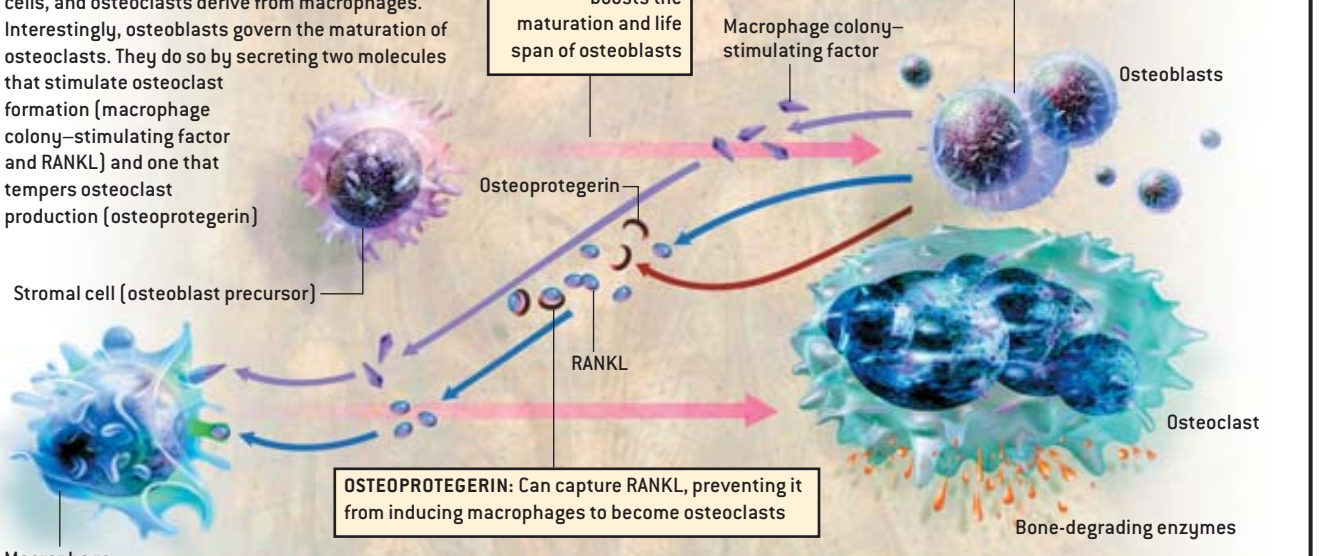


OSTEOBLAST AND OSTEOCLAST FORMATION

OSTEOBLASTS arise from precursors called stromal cells, and osteoclasts derive from macrophages. Interestingly, osteoblasts govern the maturation of osteoclasts. They do so by secreting two molecules that stimulate osteoclast formation (macrophage colony–stimulating factor and RANKL) and one that tempers osteoclast production (osteoprotegerin)

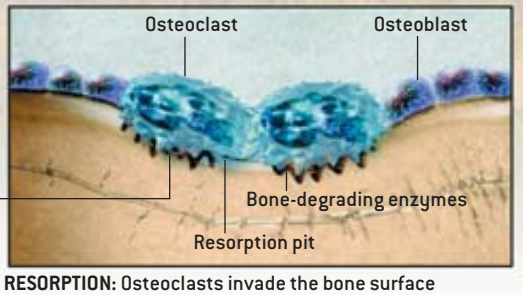
PARATHYROID HORMONE: Given intermittently, boosts the maturation and life span of osteoblasts

ESTROGEN (AND RELATIVES): Estrogen, SERMs and ANGELS prompt osteoblasts to make more osteoprotegerin. They also prolong the life of osteoblasts and kill osteoclasts



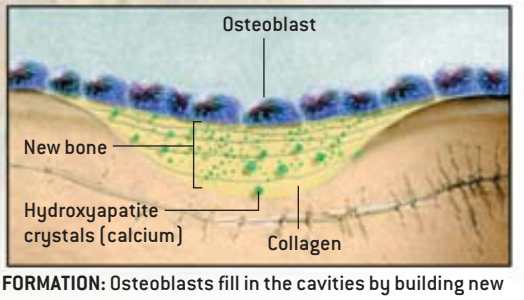
OSTEOPROTEGERIN: Can capture RANKL, preventing it from inducing macrophages to become osteoclasts

BONE REMODELING



BISPHOSPHONATES: Induce osteoclasts to self-destruct

RESORPTION: Osteoclasts invade the bone surface and secrete bone-dissolving enzymes, which carve out cavities (resorption pits) to release calcium



FORMATION: Osteoblasts fill in the cavities by building new bone. Osteoporosis occurs when osteoclasts carve too deeply or when osteoblasts fail to fill enough new bone

KEITH KASNOT

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those controls can be manipulated to encourage bone formation. In the past four years they have made progress in teasing out the features that regulate osteoclastogenesis—the birth and maturation of osteoclasts, the bone-dissolving cells.

Osteoblasts and osteoclasts both arise through the differentiation of predecessor cells in bone marrow (which also houses the body's blood-producing cells). So-called stromal cells mature into osteoblasts, and macrophages (a type of white blood cell) differentiate into osteoclasts. Recently biologists have learned that stromal cells and their offspring, the osteoblasts, govern the production of the bone-degrading osteoclasts; they do so by secreting three different signaling molecules—two that promote osteoclast development and one that suppresses it.

Early on, for instance, osteoblasts secrete a signaling molecule called macrophage colony–stimulating factor that binds to a receptor on macrophages, inducing them to multiply. A second chemical, called RANKL, secreted by osteoblasts, binds to a different receptor on macrophages, inducing the cells to differentiate into osteoclasts. The third osteoblast product, however, osteoprotegerin, can block osteoclast formation by acting as a decoy receptor—latching onto RANKL and preventing it from coming into contact with its intended receptor on macrophages.

In theory, anything that interferes with osteoclast formation—and thus with bone resorption—should enhance bone density. Research involving one intervention based on the delivery of osteoprotegerin is ongoing. In human trials, injections of the molecule have slowed the rate of bone resorption by at least 60 percent. Biologists have also identified nearly a dozen other chemical signals involved in coordinating bone formation and resorption—among them estrogen, parathyroid hormone (PTH) and insulinlike growth factor-1 (IGF-1). Study of these substances has suggested additional strategies for preventing and treating osteoporosis.

Circulating estrogen exerts its differing influences in the body by teaming up with estrogen receptors present in various tissues, including the uterus, breast, colon, muscle and bone. Doctors have known for 50 years that estrogen helps to preserve bone density, but the molecular mechanisms have long been a mystery. It is now clear that one of estrogen's functions is to interfere with the creation of osteoclasts.

More specifically, estrogen binds to osteoblasts in bone and induces them to increase their output of osteoprotegerin and to suppress their RANKL production—a combination of signals that suppresses osteoclast formation, keeping bone loss in check. The reduction of estrogen that accompanies menopause thus contributes to bone loss largely by removing an important brake on osteoclast formation and activity. In addition, estrogen appears to prolong the lives of osteoblasts while simultaneously promoting the suicide of osteoclasts. Thus, the decline of estrogen at menopause hits women with a triple whammy: shorter-lived osteoblasts must contend with more osteoclasts that have longer life spans.

In recent years, physicians had routinely urged their female patients to take hormone replacement therapy (usually estrogen combined with progestin, a form of progesterone) at menopause, not only to protect against osteoporosis but to ward off other age-related health problems for which estrogen was considered useful, including heart disease and dementia. The health benefits of hormone replacement therapy were thought to outweigh any possible dangers.

So women and their doctors were stunned in July 2002 when medical authorities overseeing the federally sponsored Women's Health Initiative determined that hormone replacement therapy caused small increases in the risks for breast cancer, heart attack, stroke and blood clots and that the risks of the therapy outweighed its modest benefits, which included small decreases in the risks for hip fractures and colon cancer. Three months later, after reviewing results from this and similar studies, the influential U.S. Preventive Services Task Force recommended against the use of combined estrogen and progestin therapy for preventing cardiovascular disease and other chronic conditions, such as osteoporosis in postmenopausal women. For now, the best estrogen alternatives for bone health are the bisphosphonates. In a meta-analysis that our group completed, combining data from many studies, the bisphosphonates proved slightly better than estrogen therapy at increasing bone mineral density and preventing fractures.

Drugs known as selective estrogen receptor modulators (SERMs) may also be useful for the long-term treatment of women fearful about breast cancer. SERMs act like estrogen in some tissues (bone, for example) while at the same time blocking estrogen's effects in other tissues, such as the breast. So far the only SERM approved for the treatment and prevention of osteoporosis is raloxifene (Evista), but others are being tested. Raloxifene is not as effective as estrogen in increasing bone mineral density and preventing fractures, and it can cause hot flashes; however, studies involving women being treated for osteoporosis have found that raloxifene reduced their risk for breast cancer.

Controlling the Controllers

BUT AN EVEN BETTER answer may be on the way. Soon scientists may begin human testing of synthetic estrogens that offer all of estrogen's bone benefits and none of the risks—and help men as well as women. Work on those agents began in response to a radical hypothesis proposed a few years ago by Stavros C. Manolagas of the University of Arkansas for Medical Sciences.

Manolagas hypothesized that estrogen exerts its effects on cells in two sepa-

THE AUTHOR

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BLAME IT ON EVOLUTION

MILLIONS OF YEARS AGO our ancestors emerged from the sea and evolved into land mammals that confronted a serious problem: how to satisfy their calcium needs, now that absorbing calcium from seawater was no longer an option.

Humans and other mammals evolved an ingenious solution to the calcium challenge, relying on our own skeletons—where 99 percent of bodily calcium resides—as calcium "banks." In a process known as calcium homeostasis, the mineral is deposited into or withdrawn from the skeleton so that blood levels are kept within the narrow range essential for nerve conduction, blood clotting, muscle contraction and other vital physiological functions. Unfortunately, this process is at the root of osteoporosis, because it calls for sacrificing the skeleton if that is what it takes to maintain adequate blood calcium levels.

The regulatory system at the heart of calcium homeostasis features parathyroid hormone (PTH), vitamin D and ingested calcium. When the parathyroid gland (located near the thyroid gland in the neck) senses a dip in circulating calcium levels, it secretes PTH—a hormone that works in several ways to boost blood calcium levels. PTH powerfully influences osteoporosis by inducing bone-degrading cells (osteoclasts) to dissolve bone and release calcium into the blood. The hormone also stimulates the kidneys to return calcium to the blood instead of excreting it and induces the small intestine to absorb calcium more efficiently from food—a feat that PTH accomplishes indirectly, by increasing the body's production of vitamin D.

Some 90 percent of the average person's vitamin D is synthesized in the skin using energy from the sun's ultraviolet rays (we also get some vitamin D from foods such as fatty fish and vitamin D–fortified dairy products). In an ongoing chemical reaction that progresses from the skin to the liver to the kidney, PTH helps to transform vitamin D3 (the vitamin D precursor made when ultraviolet rays strike the skin's epidermis) into vitamin D's most active form. Vitamin D acts directly on the small intestine, boosting its absorption of calcium from food so that more of the mineral is available for physiological functions and for bone building.

A falloff in vitamin D curtails the amount of calcium absorbed from food and causes blood calcium levels to decline, prompting the parathyroid gland to secrete more PTH to raise levels of active vitamin D. People with consistently low levels of the vitamin tend to have chronic elevations in serum PTH, a condition known as secondary hyperparathyroidism. The elevated PTH level manages to maintain vitamin D and calcium at close to normal levels but also accelerates the bone resorption that leads to osteoporosis in many people.

Recent surveys have found that low serum vitamin D levels are surprisingly common, especially among people living in northern latitudes, where sun exposure is limited. In studies involving older women, vitamin D supplements have been found effective in returning vitamin levels to normal and in preventing bone loss. I recommend that women older than 65 living in northern latitudes take 400 International Units (IU) of vitamin D daily, plus an additional 400 IU during the winter months, when bone densities tend to fall and fracture rates rise.

Ingesting sufficient quantities of calcium (1,000 to 1,500 milligrams a day) is equally important. Studies indicate that the best time for an adequate calcium intake is not later in life but during childhood and adolescence, when peak bone mass is being built. The same holds true for exercise, which is often recommended for keeping older bones healthy. When combined with adequate calcium intake, exercise—particularly jogging and other forms of weight-bearing exercise—helps to slow bone loss and may even increase bone density in older people. But studies involving young athletes strongly suggest that regular exercise—like calcium intake—exerts its major bone-building effect during youth. The higher the bone mass one attains as a young adult, the lower one's risk for developing osteoporosis later in life. —*C.J.R.*

GETTY IMAGES (*glass of milk*); JONELLE WEAVER *Getty Images (cheese)*; FRANÇOISE SAUZE *Photo Researchers, Inc. (calcium pills)*; INC. JANEART *Getty Images (woman walking)*

BONE-BUILDING ESSENTIALS include foods rich in calcium and vitamin D—such as fortified milk and cheese—or vitamin and mineral supplements. Weight-bearing exercise also keeps bones strong and healthy.

rate ways. One is the well-established mechanism by which estrogen influences *all* its target tissues in females, reproductive and nonreproductive alike: After estrogen crosses a cell's outer membrane and cytoplasm, it enters the nucleus and binds to its receptor. This estrogen/receptor duo (along with other nuclear proteins known as co-activators) directly interacts with specific sequences of DNA to induce certain genes to give rise to specific proteins needed for cellular activities.

But this "genotropic" pathway (so named because of estrogen's direct contact with genes) could not explain all of estrogen's numerous effects on cells. So Manolagas posited that estrogen also acts through a different mechanism that in-

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fluences bone and other nonreproductive tissues in both males and females and has no effect on reproductive tissues. In this scenario, estrogen still binds to receptors in cells, but the hormone and its receptor induce cellular changes by acting on kinases, enzymes that reside in the cytoplasm of osteoblasts and osteoclasts. The activated kinases then migrate to the nucleus, where they help to regulate the expression of genes.

Manolagas and his colleagues synthesized an estrogenlike hormone, dubbed estren, designed to act exclusively through the nongenotropic pathway. In 2002 Manolagas's team reported on mouse studies comparing estren with estrogen. Estren was more effective than estrogen in rebuilding bone in female mice whose ovaries had been removed to simulate menopause. Equally important, estren did not increase the weight of mice uteri, confirming the drug's lack of effect on reproductive tissue. Similar results were observed in males: estren proved just as good as testosterone in rebuilding lost bone in mice whose testes had been removed, and unlike testosterone, it had no effect on the weight of seminal vesicles.

The findings indicate that estren could become the first of a new class of osteoporosis drugs that Manolagas has named ANGELS (activators of nongenomic estrogenlike signaling). These agents might work even better than estrogen in building bone without causing estrogen's unwanted effects on reproductive tissue, such as uterine and breast cancer.

In the Driver's Seat

MUCH AS ESTROGEN defends against bone loss by limiting osteoclast development, parathyroid hormone can be considered the engine that "drives" osteoporosis, because it promotes the action of osteoclasts. PTH triggers osteoclast formation indirectly, by binding to osteoblasts and prompting them to increase RANKL output and decrease osteoprotegerin production—precisely opposite to the way estrogen regulates RANKL and osteoprotegerin to block osteoclast formation and preserve bone. Paradoxically, however, the notoriously "resorptive" PTH was approved in 2003 as the first bone-building agent, as opposed to the antiresorptives, and some data suggest that it could be the best of all osteoporosis treatments.

Although the body's own PTH promotes bone loss when elevated over long periods, intermittent injections elicit quite a different response. The first inkling that PTH could build bone emerged in 1928, when researchers noted that PTH injections increased bone density in dogs. But the finding was ignored until the 1970s, when researchers at Massachusetts General Hospital and at the University of Cambridge began experimenting with delivering natural, and later recombinant, PTH. Over the past 25 years, tests in humans have shown that intermittently administered PTH has an amazing ability to increase bone density (especially in the vertebrae), enhance the structural integrity of bone, and prevent fractures in men and postmenopausal women. Typically, daily PTH injections result in density increases of 8 to 10 percent after one year, with the risk of fracture reduced by an impressive 60 percent. Injectable PTH, under the brand name Forteo, was approved in 2002 by the U.S. Food and Drug Administration for the treatment and prevention of osteoporosis in both men and women.

Why does the body's own PTH cause bone thinning, whereas PTH "pulses" have a bone-building effect? The intermittent doses seem to direct osteoblast precursors to mature into osteoblasts while simultaneously preventing established osteoblasts from dying, resulting in much greater numbers of bone-forming osteoblasts that function for longer periods. One particular molecule activated by intermittent PTH treatment is insulinlike growth factor-1, which stimulates stromal cells to differentiate into bone-forming osteoblasts. It also circulates in high concentrations in the blood. Healthy adults have wide differences in their serum IGF-1 levels—and these can have important implications for bone density. For example, an evaluation of women in the Framingham Heart Study found that women in the highest quartile for serum IGF-1 had the highest bone density in the spine, hip and wrist.

Although diet has some influence over IGF-1 (malnutrition can cause steep declines), levels of IGF-1 are largely genetically determined. Over the past decade my laboratory in Bar Harbor, Me., has studied the genetic regulation of IGF-1 using two strains of mice that exhibit major differences in bone mineral density. Our research has shown that 60 percent or more of IGF-1 is genetically determined—a significant finding, because emerging evidence suggests that the "high normal" IGF-1 levels that protect against osteoporosis also correlate with an increased risk for breast, prostate and, perhaps, colon cancer. In the future, measuring IGF-1 levels in people may serve as a useful risk predictor, with high levels indicating a low risk for osteoporosis but an elevated risk for certain types of cancer.

In the end, the DEXA scan of Maxine's spine confirmed my suspicions. She had suffered a recent fracture of her eighth thoracic (T8) vertebra, near her shoulder blades, and her vertebral bone mineral density was more than 2.5 standard deviations below that of a 35-year-old woman. Either finding alone was sufficient for a diagnosis of osteoporosis, yet her prognosis was good. I told her that the back pain would diminish over the next several weeks. And I prescribed a bisphosphonate drug that would restore 5 to 10 percent of her bone density and reduce by 70 percent the likelihood that she would experience a fracture within the next year. The news cheered her. With more grandchildren on the way, her baby-sitting responsibilities were about to increase. SA

MORE TO EXPLORE

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spare

HOPE: A bioartificial kidney could someday end the exhausting regimen of dialysis. The prototype shown on the opposite page was developed by the University of Michigan at Ann Arbor.

Updated from the Summer 2000 issue of Scientific American Presents

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ENGINEERS ARE CREATING ARTIFICIAL REPLACEMENTS FOR FAILING HEARTS, KIDNEYS, PANCREASES AND LIVERS

parts for vital organs

BY DAVID PESCOVITZ

Atherosclerosis, diabetes, cirrhosis, hepatitis and other afflictions kill or disable millions of people every year by ravaging their organs over time. The elderly suffer the greatest toll. Bioartificial organs—a merger of mechanical parts with cells grown in laboratory cultures—could reduce premature death, improve quality of life and serve as vital bridges for seniors waiting for natural-organ transplants.

In the U.S., thousands of people die annually waiting for a transplant, and many thousands more never even make it onto a waiting list, according to the United Network for Organ Sharing in Richmond, Va., which manages the nationwide transplant network.

Engineering whole organs from scratch using pristine stem cells that can differentiate into any kind of body tissue would, of course, be the ultimate solution. But that is a longer-term prospect. For now, bioartificial organs offer the greatest hope for spare parts that can perform the complex tasks of a kidney, pancreas or liver. "We call these the smart organs," says Bartley P. Griffith, former director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh and current chief of

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NEW PUSH: The MedQuest ventricular assist device prototype propels blood through the arteries with a tiny centrifugal pump.

the cardiac surgery division at the University of Maryland. A heart simply pumps blood through one-way valves. Kidneys, pancreases and livers face the arduous task of chemically removing waste from incoming fluids and producing key compounds for the body. "If a heart is thought of as a first-grader," Griffith says, "a kidney is a senior in high school, and a liver is a postdoc."

Despite its "simplicity," building an artificial heart has proved difficult. The image of Barney Clark, recipient of the first Jarvik-7 artificial heart in 1982, was telling: his mechanical heart was connected by hoses to a large, thumping pneumatic bellows outside his body that did the actual pumping. The unit had to be plugged into the wall, limiting Clark's movement. When Clark and a second artificial heart patient, William Schroeder, died within two years as a result of infections and strokes caused by blood clots, the public's hope in the technology died with them.

It took years for researchers to rethink their approach and miniaturize components. Instead of a full-blown replacement, recent devices have attempted to assist a failing heart until a transplant can be found. The left ventricular assist device (LVAD), the foremost example, is now in clinical use. A surgeon implants it into the abdomen, where it pumps blood that has been diverted from the left ventricle, one of the heart's four main chambers that pump blood. The device is powered by a small console or portable battery pack outside the body. The LVAD solves only some heart problems and still requires a power cable that passes through the patient's skin, but it buys crucial time.

LVAD progress has renewed interest in a new generation of artificial hearts. They are smaller and more efficient because they move blood in a fundamentally different manner. Rather than pumping with flexing diaphragms, as did the previous generation, some designs have a tiny spinning impeller that propels the blood like a boat propeller moves water. The McGowan Institute used this approach in its Streamliner artificial heart, designed to be placed in the abdomen and to push blood through the natural heart and arteries using a pair of tubes. Inductive coupling could transfer energy from a coil attached to a battery worn on a belt to a secondary coil and battery implanted under the skin. The subcutaneous battery would then send power to the artificial organ over a thin wire.

The oblong Streamliner, made of titanium, is about four inches long and two inches across and weighs several ounces. It features an impeller suspended internally with magnets. "This eliminates the risk of failure because of bearings wearing out," Griffith says. The Streamliner technology has since been integrated into the HeartQuest VAD developed by MedQuest. HeartQuest, which has an even more advanced centrifugal pump, is expected to enter clinical trials within a year.

Other leading research teams are using the turbine approach in experimental LVADs. Thoratec is working with the McGowan Institute, and Micromed Technology has partnered with the Baylor Medical Center. Already more than 200 patients have been implanted with the DeBakey VAD, jointly developed by NASA, the Baylor College of Medicine and MicroMed.

Developing a "dumb" organ like the heart is a major engineering challenge, yet it pales in comparison with the complexity of building organs that have biochemical brains. To craft "smart" bioartificial organs like the kidney, pancreas and liver, experts must combine electrical, mechanical and tissue engineering. The strategy thus far is to take organ cells from humans or pigs, grow them in a culture medium and then load them into a bioreactor—a box or tube in which they are kept alive with oxygen and nutrients. The bioreactor is inserted into a larger machine outside the body. A patient's blood is diverted via tubes through the bioreactor, where it is cleansed—similar to the setup of today's kidney dialysis machines.

"Of course, the trick would be to understand the cell culture science and engineer the bioreactor well enough to implant one of these organs," Griffith notes. "I think we're 10 years away from that at least." Closer to fruition, he believes, is a "get out of trouble" bioartificial kidney, worn like a fanny pack, that could keep a patient alive during the wait for a donated human organ.

MULVEHILL *The Image Works (preceding pages)*; VA ANN ARBOR HEALTHCARE SYSTEM *(inset, preceding page)*; MEDQUEST *(this page)*

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Beyond Dialysis

DIABETES AND hypertension—the leading causes of kidney disease—plague the elderly. Today there are nearly 60,000 Americans of all ages waiting for a kidney transplant. They must undergo dialysis or hemofiltration for hours at a stretch, multiple times each week. The regimen is exhausting. Just as vexing is that the machines can do only half the task at hand. While the kidney filters urea waste products from the blood, its tubules must also reclaim 98 percent of the filtrate, returning important sugars, salts and other substances to the body. Dialysis machines just can't pull off the second step.

By combining mechanical devices with engineered tissue, a bioartificial kidney could perform the entire function. Nephrologist H. David Humes and his colleagues at the University of Michigan at Ann Arbor have grown proximal tubule cells, which handle the bulk of filtrate reclamation, from adult stem cells. (The stem cells are harvested from donated kidneys deemed unsuitable for transplant.) The cells are enmeshed along hair-thin plastic fibers that line the inside of a polycarbonate filtration cartridge about 10.5 inches long and 1.4 inches in diameter. The cartridge is housed in a larger machine. As the patient's blood is pumped through the bioartificial kidney, the engineered cells filter out urea while returning the useful compounds.

Humes founded Nephros Therapeutics to commercialize the renal assist device, and Phase II clinical trials have begun. "At this point, this is a temporary device for acute kidney failure," Humes explains. "But we're working on devices that have both filtration and a tubule element that could be wearable. We're in a prototype stage."

According to Humes, the first-generation wearable renal assist device could diminish a patient's dialysis time by 30 to 50 percent and someday possibly eliminate it entirely. "The first dialysis machine was a huge 10-by-4-foot cylinder," he says. "Our cartridges do the same thing, but you can hold them in your hand." If fabrication advances make possible even more miniaturization, he adds, his team might be able to "devise one of these for implantation."

An implantable bioartificial device to assist a malfunctioning pancreas would create a similar revolution in the treatment of insulin-dependent diabetics. At present, diabetics must follow a strict daily regimen of self-administered tests to check blood sugar levels and one or more insulin injections to pick up the slack of a weak pancreas. But "because there is no effective feedback mechanism" for the level of insulin required, injection "is done as a best guess," says Barry Solomon, senior science adviser at Nephros. The resulting large swings in glucose levels are thought to lead to the major complications of diabetes—vascular disease, retinal disease and heart disease.

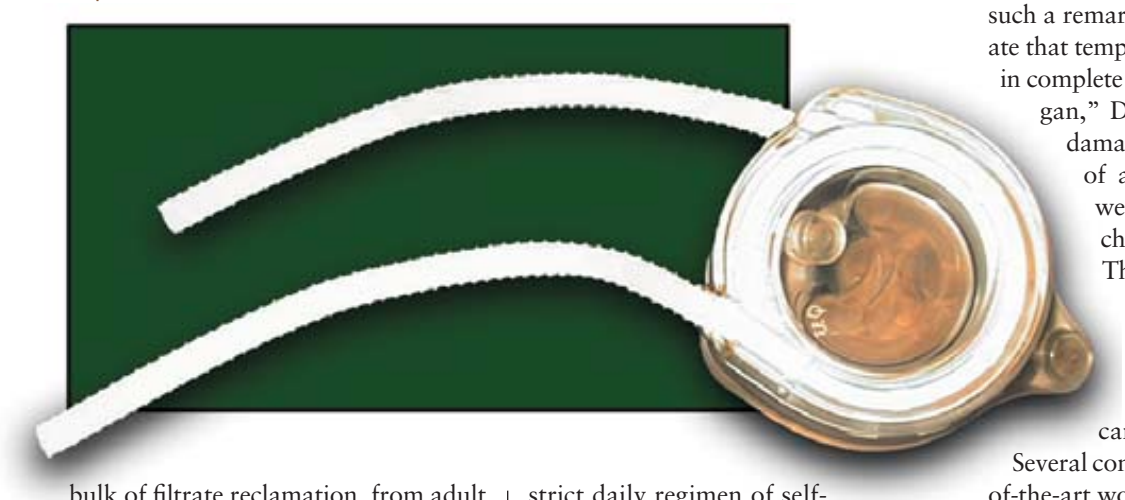
The goal is to automate the system. Existing implantable insulin pumps tend to leak, and electronic glucose sensors are notorious for failing after little more than a month inside the body. But the real shortfall is that today's systems cannot supply the feedback information needed to administer precise and properly timed dosages. Work is under way on prototype devices.

Relief for the Liver

THE CHALLENGE IS GREATER for a bioartificial liver to replace a natural one damaged by diseases and insults such as hepatitis C and alcoholism. A healthy liver metabolizes toxins, produces bile, regulates the balance of many hormones and manufactures blood-clotting proteins. Designing an organ to accomplish all these complex tasks is daunting. But a device may be needed to replace these functions only for a short time, says Achilles Demetriou, a bioartificial liver pioneer who is chairman of the surgery department at the Cedars-Sinai Medical Center in Los Angeles. "The liver has such a remarkable capacity to regenerate that temporary support could result in complete recovery of the injured organ," Demetriou points out. If a damaged liver could be relieved of all its duties for just one week, it would have a good chance of repairing itself. There is currently no machine that can take over the organ's function, however.

The goal, therefore, is a bioartificial organ that can bridge the repair time. Several companies are pursuing state-of-the-art work, including Vital Therapies, which has licensed bioartificial liver technology originally developed at Baylor. Demetriou's technology was employed in the HepatAssist system developed in collaboration with Circe Biomedical, but the company was shuttered in 2002 when the device did not meet expectations in Phase II trials. The technology is currently in limbo, but other companies reportedly may pick it up.

HepatAssist uses pig liver cells in a bioreactor to remove toxins from the



SWEET: Circe Biomedical's PancreAssist was an early attempt at an implant that would dispense insulin for diabetics.

CIRCE BIOMEDICAL

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The Cryonics Gamble

NO "CORPSES" RESIDE at the Alcor Life Extension Foundation. There *are* about 50 "patients" entombed at a rock-hard 320 degrees Fahrenheit below zero who have bet that future physicians will have the technology to "reanimate" them. When each one was at death's door, a friend or family member had phoned Alcor's CryoTransport team. The outfit rushed to the scene. Once a doctor had pronounced the subject clinically dead, the team put the deceased on ice, pumped the body full of solutions and transported it to Alcor headquarters in Scottsdale, Ariz.

The team then circulated glycerol, used as antifreeze, into the major arteries to prevent damaging ice crystals from forming among cells. The patient was then placed in a "dewar"—a tall metal thermos that is filled with liquid nitrogen. The patients stand there today in wait. But don't dare compare them to mummies. Cryonics, Alcor insists, has nothing to do with "bringing people back from the dead."

AT HER DEATH, Christine Peterson (*above*) will be frozen in a tank by Alcor, co-founded by Linda Chamberlain (*right*), in hopes that she can be revived and repaired.

Freeze now, revive later is certainly one way to attempt to extend your longevity. The first Alcor "member" has been frozen since 1976. "If you're feeling good and you enjoy life, it's not a matter of figuring out why you should do this," says Christine Peterson, a writer and Alcor subscriber. "It's more a question of why you would want to check out."

Nice theory—but there's a catch. Someone someday will have to figure out how to reconstruct your body, mind and soul. And at present neither Alcor nor anyone else knows how to do it. Therein lies the gamble.

Peterson's not worried. She believes a cure for aging will come along before she needs to be frozen. "For people around my age and younger, cryonics is more like backup insurance," she says. If a fix doesn't materialize, then she's betting that nanotechnology will bring her back from the deep freeze. Nanotechnology is one of her life's passions. She and maverick scientist K. Eric Drexler penned a book about it and co-founded the Foresight Institute, a nanotechnology educational organization. The believers say that one day thousands of nanobots—microscopic robots one billionth of a meter long—will be able to travel through your body *Fantastic Voyage*–style, repairing cells to fix whatever ails you. The army of dutiful nanobots would repair widespread cellular damage caused by the freezing, rejuvenate your brain cells and rebuild your tired old body, cell by cell, into something new.

But no one has crafted a single nanobot. And although

TIMOTHY ARCHIBALD

nanotechnology is all the rage in the popular press, many scientists ridicule molecular robots as little more than the ruminations of science-fiction aficionados.

Peterson has such faith in nanotechnology that she has signed up for Alcor's neuropreservation service—freezing just her head. It'll simply be attached to a more youthful body when it's thawed. Nanotechnology will fix any complications from her recapitation and will subsequently keep her new body youthful forever. Her mother, friends, and colleagues such as Drexler and artificial-intelligence researcher Marvin Minsky will be glad to see it; all of them are signed up with Alcor.

Putting your frozen corpse—er, body—in Alcor's care certainly doesn't come cheap. The flat fee is $120,000. Whether that's enough for the needed half a century of minding isn't clear. Charles Platt, a writer of science fact and fiction and co-founder of the CryoCare Foundation, a now defunct organization that

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IRWIN DAUGHERTY *AP Photo/Mesa Tribune*

subcontracted freezing, isn't expecting a cryonics patient to be successfully resuscitated for at least 60 years. (CryoCare's directors promise that their two patients are still in the cooler.)

If we all could be frozen and defrosted, the earth might become a crowded place. Peterson has an otherworldly solution for that, too: colonize outer space. Her vision of a space-faring society, common among her future-minded peers, is reminiscent of the late LSD guru Timothy Leary's prescription for the human race: SMI^{2}LE, an acronym for "space migration, intelligence increase and life extension."

Indeed, Leary was arguably the most famous advocate of cryonics. (Contrary to rumors, Walt Disney was cremated after his death in 1966, and Michael Jackson has never publicly announced plans to take a liquid-nitrogen bath.) But if, as English scholar Samuel Johnson noted, the prospect of one's imminent demise tends to concentrate the mind wonderfully, then eternity on ice may lose some of its allure. During his final hours of life, Leary abruptly changed his plans for cold storage. His stated reason, according to friends who were at his bedside: "Waking up in the future surrounded by a bunch of men in white lab coats holding clipboards didn't sound like so much fun." —*D.P.*

blood of patients, in a technique similar to Humes's bioartificial kidney. A cylindrical plastic cartridge 14 inches long and 2.5 inches in diameter, lined with engineered cells, fits into a larger machine. A patient's blood passes through it for cleansing. Patients must undergo six-hour sessions for seven consecutive days. "By then," Demetriou says, the hope is that either "their liver recovers and takes over or they receive a transplant."

HepatAssist is intended to serve solely as a bridge. An implantable liver replacement, Demetriou believes, will probably have to be engineered from stem cells, a venture he asserts will be "orders of magnitude more complex" than those for other organs.

In the meantime, whichever bioartificial organs emerge may face competition from other organ-replacement approaches that are also advancing, notes Peter Stock, a transplant surgeon at the University of California at San Francisco. Most anticipated, perhaps, is xenotransplantation, in which organs harvested from transgenic pigs or primates could be transplanted into humans. The organs would be endowed with certain human genes and engineered to not induce immune rejection. Various attempts to fix faulty organs by altering genes directly are ongoing.

Whether tomorrow's spare organs are built around bioartificial cartridges, pig innards or stem cells will in the end be determined by lab work and by safety and effectiveness questions that get hashed out during the FDA approval process. But no matter which technology beats the organ shortage, the ultimate prize will go to the individual who gets a new lease on life after a visit to the human body shop of the future. SA

David Pescovitz is writer-in-residence at the University of California at Berkeley's College of Engineering.

MORE TO EXPLORE

American Heart Association:
www.americanheart.org

McGowan Institute for Regenerative Medicine:
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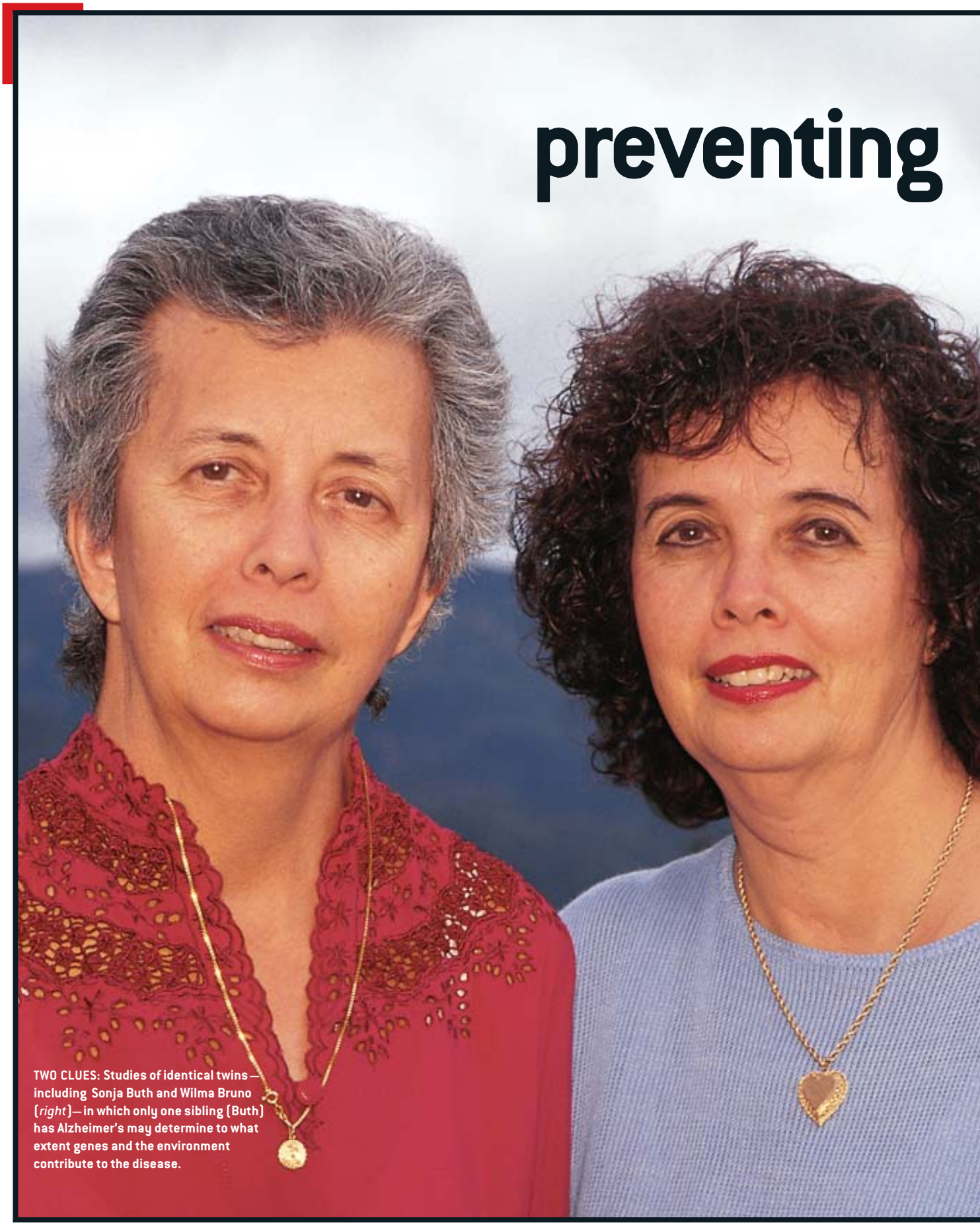
preventing



TWO CLUES: Studies of identical twins—including Sonja Buth and Wilma Bruno (*right*)—in which only one sibling (Buth) has Alzheimer's may determine to what extent genes and the environment contribute to the disease.

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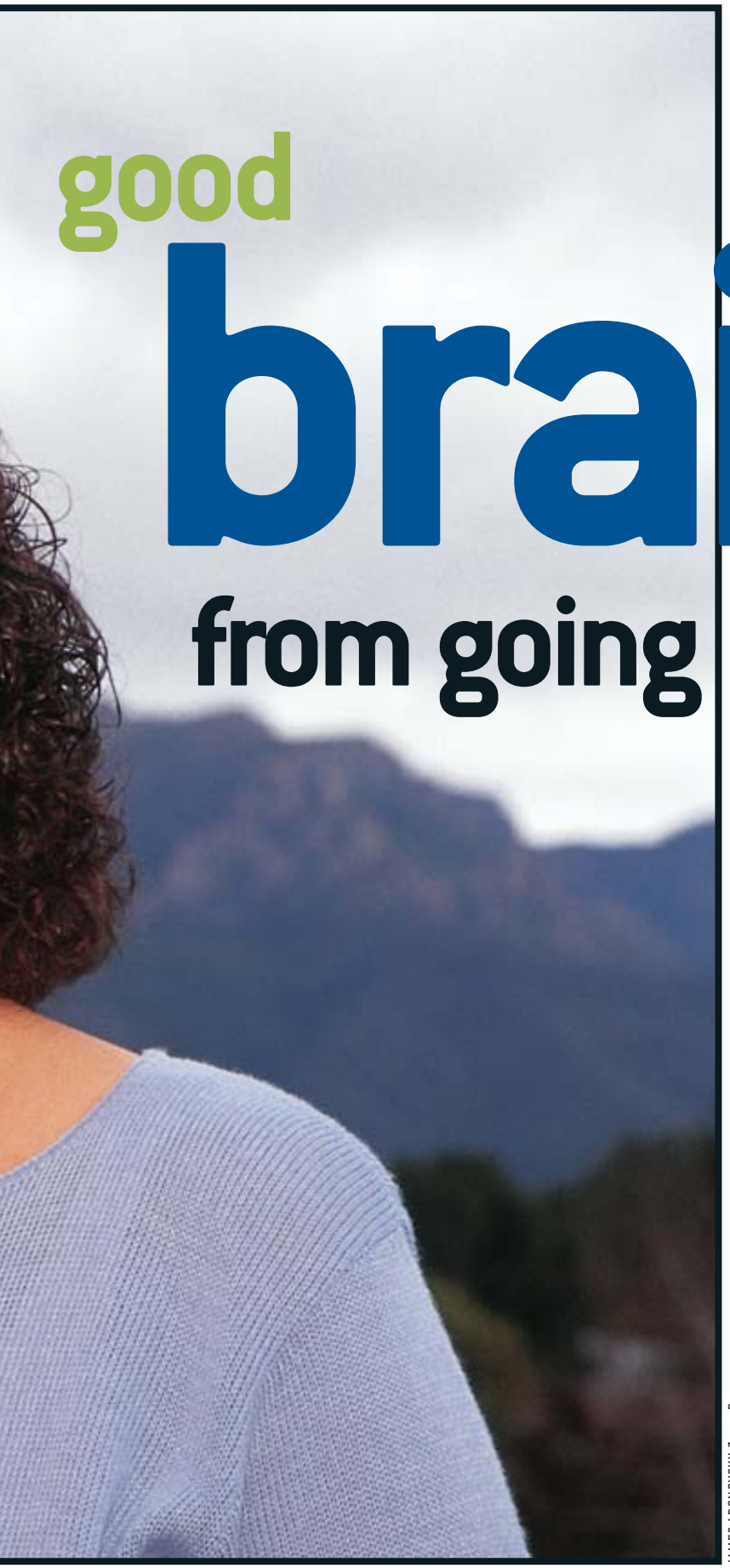
good brains from going bad

THE FIGHT AGAINST TWO LIFE-ROBBING DISEASES, ALZHEIMER'S AND PARKINSON'S, HAS JUST BEGUN

BY MIA SCHMIEDESKAMP



JAMES ARONOVSKY *Zuma Press*

It's hard to believe now, but 35 years ago the average layman *and* the average doctor thought that "senility" was the result of either normal aging or hardening of the arteries. "What do you expect from an old person?" people would say. Mercifully, science has enlightened this rather Dickensian view. Today we may be close to understanding what causes the major neurological diseases of old age, which ravage mental and physical function and in their extreme form can kill.

But that does not mean we've found cures for the four million Americans suffering from Alzheimer's disease and the one million with Parkinson's. The numbers could swell fourfold by 2040. Legions of us worship at the temples of Physical Fitness and Cooking Light, in an attempt to ensure strong bodies at retirement. But what can we do when our brains betray us?

The silent siege of Alzheimer's causes a relentless deterioration of memory and bodily control. Most Alzheimer's patients are in their 70s and beyond, and those who survive into its final stages lose the ability to speak, walk or even lift their head as

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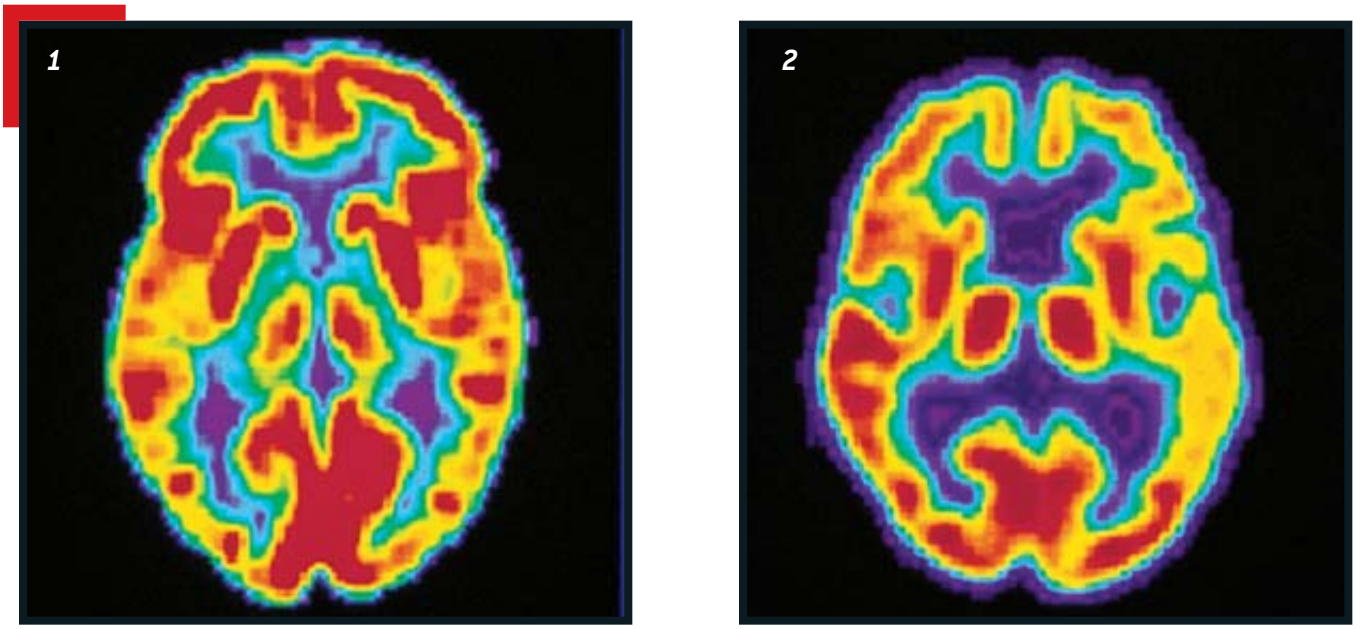

BRAIN SCAN: Reds and yellows indicate a brain's glucose metabolism. There is a progressive decrease from a normal older person (*1*) to mild Alzheimer's (*2*) to advanced disease (*3*), which resembles the level of activity in an infant's brain (*4*).

their brain slowly shuts down. Given how debilitating the physical throes are, it is confounding that the disease first appears years earlier as mental troubles such as chronic forgetfulness and difficulty handling routine chores. The onset is so elusive that doctors are only now determining where normal aging of the brain stops and Alzheimer's begins.

The borderland is a state called mild cognitive impairment (MCI). Individuals with MCI aren't demented, but they do perform worse than their peers on memory tests. They sense they are forgetful, and somebody close to them has probably noticed it, too. Otherwise, they do quite well, although demanding tasks such as mastering new technology may prove challenging.

People who meet the criteria for MCI will evolve to clinical Alzheimer's at a rate of 10 to 15 percent a year, according to Ronald C. Petersen, director of the Mayo Alzheimer's Disease Research Center. "That's in contrast to normal elderly people"—without MCI—"who do so at a rate of 1 to 2 percent a year," he says. Barry Reisberg, clinical director of the Silberstein Aging and Dementia Research Center at New York University, finds similar trends. When he tracked people with MCI in their early 70s, about two thirds progressed to Alzheimer's within four years.

Images of the brain can help pinpoint those most at risk. The hippocampus—a structure closely tied to memory—atrophies and shrinks in Alzheimer's patients. The decline is evident even during MCI. Someday a combination of memory tests and brain imaging may offer early warnings to those destined for Alzheimer's—valuable information if drugs are developed that can prevent the disease or stop its progression.

Elderly people who feel forgetful but perform well in cognitive tests—Petersen refers to them affectionately as "the worried well"—develop Alzheimer's at much lower rates, about 12 percent over four years in Reisberg's study. All that's necessary, Reisberg says, is "to reassure them."

Older people these days do seem quick to diagnose themselves or loved ones as having Alzheimer's when they are just experiencing simple forgetfulness. The knee-jerk response is in part the result of stepped-up media coverage.

So what *should* set off alarms? Failure to remember important items with increasing frequency, Petersen says—"things that you would have remembered without question six months ago"—especially if other people also say they see a change in you. "It's not that you misplaced your keys," adds Richard Mohs of the Mount Sinai School of Medicine. "It's that you can't figure out what you would do to get them back."

Mohs points out that everybody gets forgetful with age. "The rate at which people can put new information into memory does slow down. When they say, 'I forget more,' it's usually that they just didn't learn it quite as well." Elderly people can boost memory by taking extra care to learn new information.

Rays of Hope

ONCE ALZHEIMER'S is diagnosed, families can brace for the future, but the medical profession finds itself at something of a loss. Neurotransmitter-boosting drugs such as donepezil help about 50 to 70 percent of patients, according to Peter Rabins of the Johns Hopkins School of Medicine, but their effects are modest. Rabins says, "I ask families to think back to what the person was able to do seven or eight months ago; that's an average improvement." Although this reprieve is precious, it's unclear if any improvement can last longer than a few months. Memantine, approved late in 2003, offers modest benefits to severely disabled patients. For now, man-

GARY SMALL AND MICHAEL PHELPS *U.C.L.A. School of Medicine*

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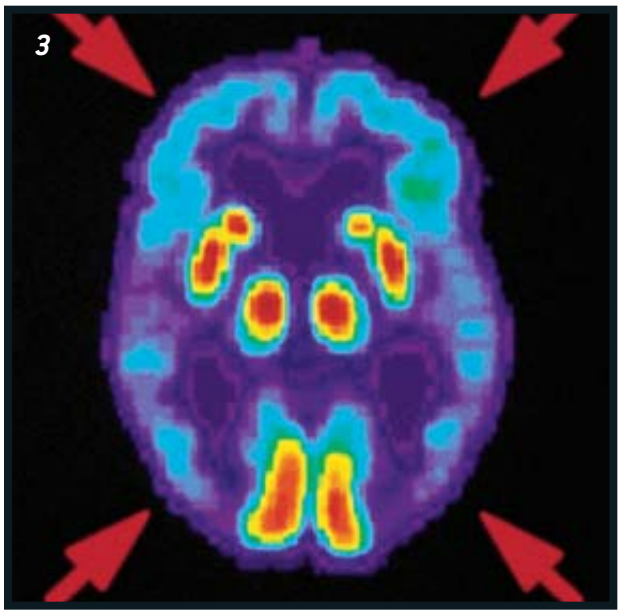

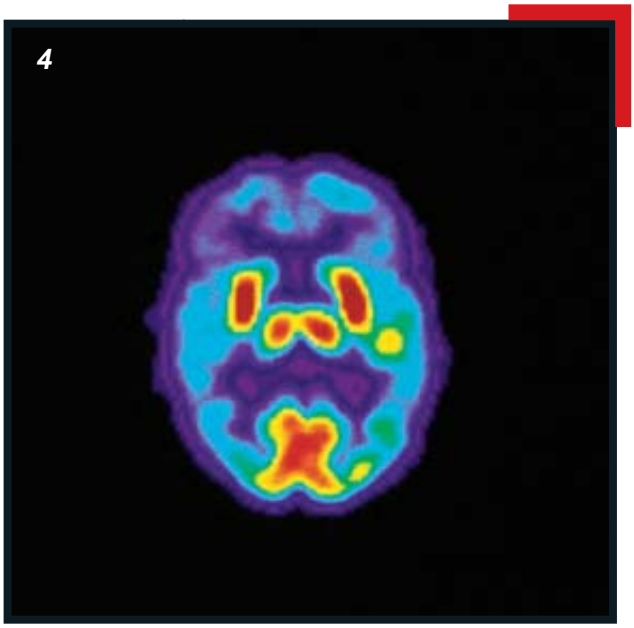

aging Alzheimer's consists mainly of emotional and practical support, plus strategies to help patients retain skills and live a full life [*see box on next page*].

With few treatment options, prevention is key. Various studies, including a landmark University of Kentucky study of elderly nuns belonging to the order of the School Sisters of Notre Dame, suggest that the brain's ability to resist dementia is greater if it has been mentally stimulated throughout life. "If you don't use it, you lose it," exhorts University of Kentucky neuropathologist William R. Markesbery.

Richard Mayeux, co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University, also finds that people with complex jobs have reduced risk of Alzheimer's no matter their education—suggesting again that intellectual challenge throughout life is important. Mohs recommends exercising the brain by reading, taking classes and joining intellectually engaging clubs.

Caring for the body is a good idea, too. People who are aerobically fit tend to suffer less cognitive decline with normal aging. Intriguingly, when Fred H. Gage of the Salk Institute for Biological Studies in La Jolla, Calif., allowed mice to run at will—about five kilometers a day on average—they generated many more new neurons in their hippocampi compared with their cage-potato counterparts. Others have found that prolonged stress actually leads to hippocampal atrophy.

Many of the School Sisters nuns donate their brains to the University of Kentucky's Sanders-Brown Center on Aging; Markesbery, the center's director, has examined them and others. One remarkable thing he sees are organs rife with the lesions characteristic of Alzheimer's—from individuals who were not demented.

Perhaps these brains had something extra in reserve, or maybe they avoided stroke. Dementia from vascular disease alone is fairly uncommon in the U.S. But among nuns with the brain lesions of Alzheimer's, those who also had tiny strokes were more likely to be demented. To lessen the risk of stroke, Markesbery advises people to eat right, exercise, not smoke, and keep blood pressure and diabetes under control—good advice in any case.

Other promising leads come from studies of identical twins. In the early 1980s John Breitner, now at the University of Washington, helped to show that Alzheimer's disease aggregates in families: "If you could follow hypothetical relatives of somebody with the disease, let's say siblings, out to age 90 or 95, then almost half those siblings would themselves get the disease—a much higher rate than in the general population." To tease out how much of this aggregation is a result of genetic inheritance, rather than shared family environment, several groups studied the occurrence of Alzheimer's in identical and fraternal twins. The studies suggest that one half to three fourths of a person's disposition to Alzheimer's is inherited. But that leaves plenty of room for outside influences.

While at Duke University, Breitner and his colleague Brenda Plassman focused on twin pairs in which only one twin had Alzheimer's. The disease often develops in the initially unaffected twin after a lag, but in some identical pairs the second twin remains free of disease for as long as two decades after it appears in the first. The researchers studied the histories, lifestyles, infirmities and medications of many pairs. "What surprised us," Breitner says, "was an unexpected association between use of anti-inflammatory drugs and the absence of disease in the unaffected twin."

Other studies of medication use have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are associated with reduced risk of Alzheimer's. The medical community is now awaiting results from clinical trials. There are several ongoing tests of NSAIDs, donepezil, vitamin E and ginkgo biloba in people without Alzheimer's,

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Coping with Alzheimer's

Talk of an eventual cure for Alzheimer's generates a lot of excitement, but millions of people must deal with the devastation of the disease right now. Much depends on creative coping.

Barry Reisberg of New York University has studied the course of Alzheimer's for more than two decades. He argues that the characteristic decline can be understood best as a reversal of childhood development. The sufferer incrementally loses the ability to handle finances, then to dress, then to be continent, speak, walk and sit up.

This view must be handled with caution so that the adults are not infantilized. But it may be useful in guiding caregivers. "A [late-stage] Alzheimer's patient requires the same amount of care as an infant," Reisberg says, and he doesn't mean just feeding and bathing. "You would read to an infant; you should be reading to the [late-stage] Alzheimer's patient, too." What the Alzheimer's sufferer needs most is attention and activity. Simple exercise reduces agitation. Visiting them when they get restless at night calms them down.

About two thirds of Alzheimer's patients are cared for at home by family, according to Peter Rabins of the Johns Hopkins University School of Medicine. This can be tough. The founding of the Alzheimer's Association in 1979 focused resources to help those family members, he says. What the families need is practical assistance: an aide to help with bathing, day care so the breadwinner can work, and emotional support.

Teaching families specific coping strategies can alleviate depression—among patients and caregivers alike. "Oftentimes it's just become this stressful, difficult situation," says Linda Teri of the University of Washington. "The patients can't do things they used to enjoy, they get frustrated, and the caregivers may not understand what they still like to do."

One important focus is identifying appropriate pastimes. The family members of one former professor with Alzheimer's discovered a pleasant, stimulating activity after recalling how much he loved doing the *New York Times* crossword puzzle. They found a variety of children's word puzzles that he could still handle. "You give caregivers strategies, ideas," Teri says, "and they come back and say, 'We had a nice day yesterday. We haven't had that in a long time.'" —*M.S.*

NEW DAY: Patients with advanced disease relearn basic skills at the Maria Wolff Alzheimer's center in Madrid.

MARIA WOLFF ALZHEIMER'S CENTER

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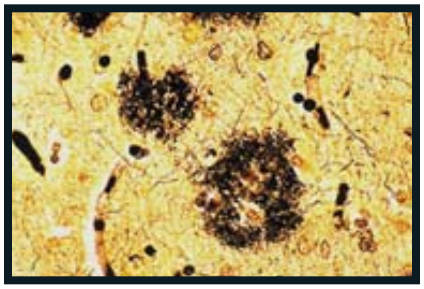

PLAQUES OF ALZHEIMER'S DISEASE (*darker regions*) are readily apparent when brain tissue is treated with a silver stain. The tangles are most numerous in the cerebral cortex and hippocampus regions.

COURTESY OF EDWARD C. KLATT *Florida State University College of Medicine*

who either have MCI or are cognitively normal. As for treatment, results are showing that NSAIDs aren't effective for changing the course of Alzheimer's once it has taken hold.

Prevention data from MCI trials are expected soon, but studies of cognitively normal people may take many years to complete. Breitner is running an NSAID study with an over-the-counter dose of naproxen and an antiarthritic dose of celecoxib in people without MCI. "It's a long, hard battle to do this trial," he says. "It's going to take the rest of this decade to get the results that we need."

The controversy over the benefits of hormone replacement therapy underscores the importance of patience in awaiting clinical trial results. Just three years ago it appeared that the use of hormones to prevent dementia in elderly women might be worthwhile. This suspicion was based on several observations that Alzheimer's sufferers were less likely to have had hormone replacement therapy following menopause than peers who didn't show signs of the disease.

With the end of the Women's Health Initiative Memory Study (WHIMS) in 2002, however, a new attitude has begun to emerge. "Older women taking estrogens with the idea that they're going to be preventing the risk of Alzheimer's disease and dementia is not a good idea," Breitner explains. WHIMS tested the effects of estrogen and progestin replacement in women over the age of 65, and the researchers concluded that for these older women the hormones increased the risk of dementia. They also found no evidence indicating that the hormones prevented MCI in this group.

With other results showing that hormone use in older women does not prevent heart disease and slightly increases breast cancer risk, hormone replacement therapy is increasingly reserved for management of symptoms such as hot flashes in women near the time of menopause. It is not completely clear how hormone use limited to that stage might impact Alzheimer's risk. Some data, including a study Breitner recently published about citizens of Cache County, Utah, suggest that although women in their 80s and 90s who are using hormone replacement therapy don't have a lower Alzheimer's risk, women that age who had used such therapy for at least a decade in the past might have a lower risk.

In the end, doctors and patients are still left wondering how to ward off Alzheimer's disease. "In my own practice, I don't recommend taking any drug for the principal purpose of preventing cognitive decline," says Eric B. Larson, a physician and longtime Alzheimer's researcher at the University of Washington. "There's nothing out there that's convincing enough."

Anti-inflammatory drugs may reduce risk of Alzheimer's.

New insight may come from the mechanisms underlying Alzheimer's disease. The theory most drug companies are pursuing is that the villain is a protein fragment called Aβ that clumps into plaques in Alzheimer's-affected brains. Aβ results when enzymes snip a protein called amyloid into pieces. Aβ is present in everyone, and no one is sure what it does, but when disposal of Aβ can't keep up with its production, trouble may loom. Genetic mutations that cause rare early-onset Alzheimer's increase the production of Aβ, whereas genes altered in some late-onset disease may be important for clearing Aβ.

Mice that overproduce Aβ develop Alzheimer's-like plaques. Immunizing them against Aβ prevents the appearance of new plaques and also reduces the extent of existing ones. In 2001 an Aβ vaccine trial in Alzheimer's patients was stopped after a few weeks because about 6 percent of the subjects developed brain inflammation. Despite the setback, data published from Swiss study participants suggest some slowing of cognitive decline after the vaccine, with the amount of slowing correlated to the amount of Aβ antibodies.

Dennis Selkoe of Harvard Medical School, long on the trail of Aβ, recently determined what part of the vaccine peptide can cause inflammation, and he thinks that trials with a version lacking this segment are feasible. "The same companies have made a shorter Aβ vaccine and tested it in animals," he says. "They're hoping the [Food and Drug Administration] will allow them to try that in Alzheimer's patients." He says another company is testing Aβ antibody as a potential Alzheimer's drug.

Early promising research on inhibitors of gamma secretase, an amyloid-snipping enzyme, has since met with disappointing side effects in animal trials. It turns out that gamma secretase has vital cellular responsibilities beyond producing Aβ. Selkoe still has hope for that field, however, noting that there is another enzyme involved in Aβ production and that certain NSAIDs alter gamma secretase activity (albeit at high doses), offering leads for future research. "Drug companies are working 24 hours a day, and so am I," Selkoe explains. "My wife says, 'Why don't you get going—you're going to get the disease before you cure it.' I don't want that to happen."

Calming Parkinson's

STRONGER SIGNS of hope for fighting neurodegenerative disorders may be

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Deep brain stimulation has caught on like wildfire.

found in the history of treatment for Parkinson's disease, which strikes at age 60 on average. With no reliable treatment decades ago, its onset often meant a quick decline to years of disabling tremors and rigidity. There has since been some success with a drug called levodopa. The first whisper of tremor, or a slightly odd gait, means that a Parkinson's sufferer has already lost 70 or 80 percent of a tiny segment of the brain that churns out the signaling chemical dopamine. Without dopamine, neurons that control motor activities go haywire, leading to shaking, slowness and rigidity. As more and more dopamine-producing neurons die, sufferers can develop balance problems, crippling distortions of the hands and feet, and episodes of freezing in midstep. Late-stage Parkinson's often means confinement to bed and wheelchair.

SILENT SHOCK: Electrodes inserted deep into the brain deliver current from a battery implanted near the collarbone to quell the symptoms of severe Parkinson's disease.

Levodopa can't halt the progress of the disease, but it can replace missing dopamine, with miraculous effect. Many of those afflicted with Parkinson's are symptom-free after their first dose. Doctors started relying on the drug in the late 1960s, and today it is almost universally prescribed. "Levodopa was really one of the great biological successes of the century," says C. Warren Olanow of Mount Sinai.

Like most classic heroes, though, levodopa has a dark side. At first, its benefits last hours on end, but after five or 10 years many patients take levodopa much more frequently and still can't get a consistent effect. "You could be in a grocery store, reaching into your purse to pay, and all of a sudden you go 'off'—you can't move, and you don't know when you're going to come 'on' again," says neurologist Jerrold Vitek of Emory University. "One patient told me about being bent over his couch to pick something up, and he froze like that for two hours." Many people also develop involuntary motions in response to the drug.

The new challenge of Parkinson's treatment is to smooth out levodopa's effect or retire the chemical altogether. One long-standing strategy is pairing levodopa with other drugs. Some compounds ensure a richer stream of levodopa to the brain. Others act to delay the need for levodopa therapy as long as possible.

Then there is brain surgery. For years surgeons have been able to burn tiny holes in the brain, destroying specific areas that go awry in Parkinson's. Although patients get some relief from tremor and rigidity, the ablation, which is irreversible, has drawbacks. For example, operating on both sides of the brain can cause unacceptable cognitive changes, whereas unilateral surgery leaves one side of the body with Parkinson's symptoms.

Lately, ablative surgery has given way to a reversible technique called deep brain stimulation (DBS). Surgeons insert electrodes deep into the brain, typically on both sides. Powered by batteries implanted near the collarbone, the pulsing electrodes orchestrate a normalization of neuronal signaling.

DBS can turn some patients' lives around. Before having the new surgery in 1998, when he was 79, Vern Setterholm's Parkinson's disease had advanced to such a degree that he had trouble handling silverware, dressing himself, even shaping his face into a smile. With DBS, the tremor in the retired executive's right hand went away, he could grin again, and he even enjoyed exercise class a few times a week. Asked whether he'd have this new kind of brain surgery again, Setterholm shot back, "If they wanted me tomorrow, I'd be there."

Olanow says he has patients who are "totally unable to be controlled with medicine. They are frozen, cannot move. We turn on the stimulator, and they get up and start walking. It's absolutely amazing."

A more advanced DBS is now available, approved by the FDA in 2002. Since then, Vitek notes, "it's caught on like wildfire." There is debate about how

MICHEL F. LÉVESQUE *Cedars-Sinai Medical Center*

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early to start DBS, however, and the procedure is currently reserved for patients who are no longer responding well to medication—"those at the end of the rope," Vitek says. Many patients actually cut back on medication after surgery, reducing some of the problematic involuntary movements that are common side effects of levodopa. Neurologists are now looking to refine DBS technology. Starting in mid-2004, Vitek will co-direct a new program at the Cleveland Clinic, where physicians, engineers and computer modelers will search for the patterns of stimuli and brain targets that work best.

The next dream is replacing the dopamine-producing neurons that die in Parkinson's. In one experimental approach tried at several research centers, surgeons transplanted human fetal neurons that produce dopamine into the brains of Parkinson's patients, hoping to restore some normal dopamine manufacture. The results have been disappointing so far, however. Recent trials have shown no significant benefit for Parkinson's symptoms, and in one study more than half of the transplant recipients developed involuntary, rhythmic movements of the lower extremities.

The results with fetal cells have left researchers asking if stem cells from the patient's own brain might produce a better result. This notion was outlandish just a few years ago, before scientists proved that even adult human brains generate new neurons from precursors known as stem cells. Gage of the Salk Institute says of his experimental work with animals, "We and others have shown that if you take primitive cells from a lab culture, you can actually put them into parts of the brain that are damaged, and they can turn into cells that are appropriate for whatever is happening in that part of the brain."

Researchers are eager to harness this potential to treat diseases like Parkinson's and Alzheimer's. The hope is that a patient's own stem cells might be better behaved (and less likely to be rejected) than transplanted foreign cells. Michel F. Lévesque of the Cedars-Sinai Medical Center in Los Angeles has looked for such stem cells in his patients. From a snippet of brain taken during surgery, he says, "we are able to identify about 10 to 15 neural stem cells on average." What might be done with the cells, however, remains an open question.

KAMENKO PAJIC *AP Photo*

VISIBILITY: Awareness of Parkinson's has been raised by public figures, such as former U.S. Attorney General Janet Reno, who have disclosed that they are battling the disease.

Perhaps the only breakthrough more exciting than giving people a shiny new set of dopamine-producing neurons would be helping them keep the originals. But no one knows what causes Parkinson's disease. The idea of a toxin is intriguing. In the 1980s drug addicts who shot up with designer drugs contaminated with a poison resembling a pesticide started suffering from the classic symptoms of Parkinson's. Vitek says that although some patients seem to be genetically predisposed to acquire the disease, it's also possible that "exposure to an environmental insult gets the ball rolling." The details remain a mystery.

Researchers are busy testing hundreds of drugs, hoping to toss a molecular monkey wrench into whatever process kills the neurons. Several medicines have been suspected of slowing the damage, including drugs called dopamine agonists, which are widely used before or with levodopa. Another drug, selegiline, delayed levodopa therapy about nine months in a study of early-stage Parkinson's patients. It's not clear whether the effects are simply a result of relieving symptoms rather than preventing the underlying damage. "But there is no question that selegiline slowed the appearance of disability in Parkinson's patients," says Olanow, who sat on the study's steering committee. Whether for treatment or prevention, that's good news. SA

Mia Schmiedeskamp is a Seattle-based freelance writer who holds a Ph.D. in biochemistry.

MORE TO EXPLORE

Alzheimer's Disease: A Guide for Families. Lenore S. Powell and Katie Courtice. Perseus Press, 1993.

The Alzheimer's Association outlines strategies for coping and has details of treatment at **www.alz.org**, or call **800-272-3900**.

The American Parkinson Disease Association offers information on treatment and helping patients at **www.apdaparkinson.com**, or call **888-223-2732**.

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WHETHER OLD AGE IS WORTH LIVING DEPENDS LARGELY ON MENTAL HEALTH

BY CATHERINE JOHNSON

promised land or purgatory?

Updated from the Summer 2000 issue of Scientific American Presents

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Isn't it great that we're all going to live to 100? Sure… if we can stay healthy that long. Will greater longevity mean 30 years of quality old age or a 30-year purgatory of pain, disability and isolation? Most of the scientific work on aging concerns the physical body—genes, cells, organs, and plaques in the arteries and brain. As our bodies last longer, however, we face an increasingly daunting challenge to psychological well-being. Even if we *live* through bone loss, hearing decline, arthritis, heart trouble, cancer and a weakened immune system, the daily battles threaten to wear down our spirit.

ED KASHI

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Indeed, with a growing arsenal of countermeasures to the physical ailments of aging, quality old age will depend more and more on good mental health. And that's a tough nut to crack, because age weakens our minds as much as our bodies, severely challenging our ability to remain mentally acute and emotionally positive. There is hope: science is beginning to provide clues about how to overcome the major mental challenges of old age.

Battling Depression

PEOPLE ARE NOTORIOUS minimizers of unpleasant realities. As University of California at Los Angeles psychologist Shelley E. Taylor and others have shown, "positive illusions" are a standard feature of the psychologically healthy person. On the face of it, there's no reason why people shouldn't simply continue deluding themselves into old age. Many do. When very old and sick people are asked whether they would rather live one year in their current condition or die sooner in good health, they choose quantity over quality.

Still, choosing to live rather than dying is a far cry from enjoying a life that is happy or even marginally satisfactory. The truth is, the elderly suffer very high rates of depression compared with the rest of the population. Old age can be a mental grind.

Boston psychiatrist John J. Ratey, author of *A User's Guide to the Brain,* sees a number of elderly patients in his practice. "Loneliness is a huge issue for them. They don't interact as much. They get a little depressed because they're losing people, structure, function and purpose." Add the physical challenges, and a negative feedback loop begins to spiral. They don't feel like doing *anything* productive, physically *or* mentally. As Ratey observes, "They're losing energy, arousal and vigilance. Going into retirement, the large majority of people think, 'Oh, I'm going to have so much time to do stuff,' and then they end up watching TV. Nonaction begets nonaction—these older people don't move enough and slide into lethargy."

A global state of mental and physical torpor is not much of a life. But snapping out of depression by means of self-generated positive illusions gets harder, because with advanced age, positive illusions become difficult to sustain.

No one knows precisely why this is so, but researchers believe that age-related changes in the serotonin system play a key role. Serotonin is the neurotransmitter most closely linked to feelings of happiness, confidence and calm, and it declines with age. Although the neurological basis of emotion is far more complicated than the relative level of one neurotransmitter, researchers nonetheless find that people with low levels of serotonin are more likely to feel depressed, anxious or angry. Carolyn Meltzer, vice chair of radiology research at the University of Pittsburgh School of Medicine, has found a 55 percent reduction in serotonin receptors in older subjects. Aging women suffer the further complication of a sharp decline in estrogen after menopause. Estrogen is a precursor to serotonin in the brain.

Battling depression becomes harder

THE DANGERS OF OVERMEDICATION

By the time the average American has turned 70, the seven-day pill organizer may be overflowing with colored capsules. As medicine finds more fixes for the maladies of old age, the elderly are in danger of becoming increasingly dependent on scores of pills, reducing their quality of life and potentially killing themselves via overdose or unintended drug interactions.

The Golden Years are exactly the wrong time to face a panoply of pills. Neither our memories nor our kidneys are up to processing half a dozen different prescriptions half a dozen times a day. It's just too easy to mess up (as this author—a long way from "elderly"—discovered one morning when she took her aging dog's medication instead of her own).

One major cause of the problem is polypharmacy, the prescribing of numerous drugs by different doctors for the same person, often for the same disorder. The marketplace is also implicated. "The elderly obtain drugs from many different sources—over the counter, their local pharmacies, and mail-order sources their insurance companies mandate," notes Joseph J. Bova, owner of Cary's Pharmacy in Dobbs Ferry, N.Y. "They can end up receiving the same medication with different names and not realize they are taking it twice."

CORBIS

CONTRAINDICATION: Too many pills can confuse or harm.

Brian White, a registered nurse at the Community Hospital in Dobbs Ferry, says senior citizens are routinely admitted to the emergency room who are in grave danger from overdoses of necessary medication. And it doesn't even take an overdose to cause life-threatening complications. "As you get older, you don't metabolize drugs as efficiently," White explains, "so medications can build to toxic levels in the blood. Just being dehydrated

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still because the elderly find themselves in the constant company of death. Old people lose friends and loved ones at rates far higher than the rest of us. And when you're 90, you know that your own death is likely to be close.

Reducing Stress

MAYBE THE MOST ironic fact concerning the neurology of aging is that while practically every other significant hormone in the body declines precipitously with age, cortisol, the stress hormone, shows no drop-off whatsoever. In fact, old people may show *more* sustained cortisol production when subjected to stress tests. Apparently, we simply cannot exhaust the body's ability to flood itself with cortisol when life gets hairy.

This sounds like some malevolent Greek god's idea of a joke. If so, it gets funnier: the body's ability to *recover* from stress diminishes with age. The stress from a virus, an argument with a friend or a dip in a cold swimming pool stays with you longer when you're old than when you're young. As we age, we get better at becoming stressed and worse at letting stress go.

Lower levels of serotonin combined with higher levels of cortisol make for a harsh cocktail. This is the very hormonal makeup found in clinically depressed young people. Yet researchers are not sure how meaningful this resemblance might be. Owen M. Wolkowitz, professor of psychiatry at the University of California at San Francisco, points out that although the elderly may have higher cortisol levels, they are still within normal limits. The real villain might be a drop in DHEA, a hormone that regulates the effects of cortisol. "DHEA drops with age," Wolkowitz says, "although the amount of decline is highly individual. But it's probably the ratio of DHEA to cortisol that matters. When the ratio declines dramatically, that may be especially problematic." The "grumpy old man" view of the aged takes on new meaning considering the hormonal state elderly men (and women) often endure. If your balance of cortisol is off, those crying children in the supermarket can be *really* irritating.

Here again, negatives beget negatives. A person whose stress response system is permanently stuck on high will develop strategies designed to limit his or her exposure to stress—strategies that are likely to result in even less involvement with the social world than the individual's fading energy has already decreed.

Stanford University neuroscientist Robert M. Sapolsky observes that when old people are faced with a difficult situation, they are more likely than younger people to distance themselves from it. It may be that the intense stress reaction, accompanied by slow recovery time, makes the cost of a direct approach to life's stressors too great. Withdrawing from society, however, is one of the worst things an elderly person can do; study after study has shown that social support and active engagement with other people combat depression.

Taking Charge

FORCING YOURSELF to fight depression and stress requires initiative and planning. But the single most fundamental change gerontologists see in the normal aging brain is a 5 to 10 percent loss of tissue in the frontal lobes, which are largely responsible for these very skills, notes Mony J. de Leon, professor of psychiatry at the New York University School of Medicine. Although the brain declines slightly in size overall, no other part undergoes a change of this magnitude.

The frontal lobes are the seat of what neuropsychologists call "executive function" (EF), a cognitive capacity defined in the 1990s. Executive function is a person's ability to plan, organize time, stay focused and motivate oneself. Any degree of impairment to EF is going to hamper an elderly person's ability to ward off depression by creating an active, purposeful and structured existence—or even to want to do so. Ratey observes that for all people, a sense of purpose in life—a mission—is essential to happiness as well as to good brain function.

An impaired EF can also interfere with an individual's ability to establish and maintain social support. Motivation to see friends and family may wane. Unattractive personality traits may arise, making others less inclined to spend time with that individual, because another EF function is impulse control. The "grump" was there all along, but it was controlled. Now the older person can no longer manage this behavior.

Stimulants may help counteract brain deficits such as frontal lobe loss. Ratey and his colleagues sometimes treat the loss of energy associated with advanced age with Provigil, a novel compound approved in 1998 for the treatment of narcolepsy. No one has pinned down exactly how Provigil affects brain cells, but it has been shown to promote alertness. Ratey describes one patient as "an 86-year-old woman who would have to return to bed for hours each day because of tiredness. Now she is 'thrilled' with a restored energy level and sense of well-being. Instead of being slumped over in bed, she is reading, catching up on her correspondence and exercising." Ratey has also found that Provigil can counteract the sedation that often accompanies the many medications taken by seniors. Soon the elderly may routinely be given medications like this to treat frontal-lobe deficits.

can cause a dangerously high level."

Better drug management strategies are the key to safety. Bova cites the Brown Bag program sponsored by Meijer Stores (www.meijer.com/pharmacy/bb.asp) as one approach. "Patients bring the contents of their medicine chests to a participating pharmacist for his review," he explains. "He can pick up problems such as duplication of drug therapy and help avoid mistakes."

Ultimately, though, advances in medicine itself will provide the best solution. Researchers anticipate that the Human Genome Project will help us discover hidden links among disorders we have traditionally viewed as distinct. If, say, we find an underlying genetic link among heart disease, Type II diabetes and high blood pressure, it's possible we'll need only one highly refined medication to treat them all.

Until then, if you're elderly, keep the organizer organized, and if you're not, offer to help someone who is. *—C.J.*

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Mental Exercise Pays Off

IF BY NOW YOU'RE becoming depressed and stressed about the prospects for a mentally healthy old age, cheer up. Help may come from sustaining simple daily habits in our lives. The key tactic is to keep challenging the brain.

Although some decline in hormones is inevitable, significant mental decline is not. All people, beginning in their 20s, show a gradual slip in mental faculties on neuropsychological tests, but the slope of decline varies dramatically. Moreover, as the existence of people such as Federal Reserve Board chair Alan Greenspan, age 78, should make clear, it is entirely possible for a person of advanced years to function better cognitively than many people do in their 30s.

Such acuity is testimony to one of the most fundamental research findings of the 1990s: that neurons and their interconnections can remain remarkably plastic into a person's 80s and beyond. The brain is not a preset, unalterable network of cells. Aging connections can remain flexible, and new ones can even be formed, regardless of how old that gray matter becomes. This is extremely important because it indicates that the brain can reroute connections around areas that may be growing rigid with age or even bring those areas back to greater functionality.

"The brain remains plastic until death," says Arnold B. Scheibel, a robust 81-year-old professor of neurobiology and psychiatry at U.C.L.A. and former director of the Brain Research Institute. "With plasticity we can short-circuit evolution. We can force ourselves to evolve within our own lifetimes."

Scientists are only beginning to understand how we can maintain our brain's plasticity, but a few promising avenues have been found. Physical exercise is one. Although the mechanism has not been pinned down, the physical exertion of the cardiovascular and muscular systems seems to keep the brain more pliable. One study shows that aerobic walking improves executive function in people between the ages of 60 and 75, and there is no reason to believe that this would not hold true for 80- and 90-year-olds. The subjects' ability to switch rapidly from one task to another improved, their distractibility decreased, and their ability to *stop* doing whatever they were doing (like taking their foot off the accelerator while driving) increased.

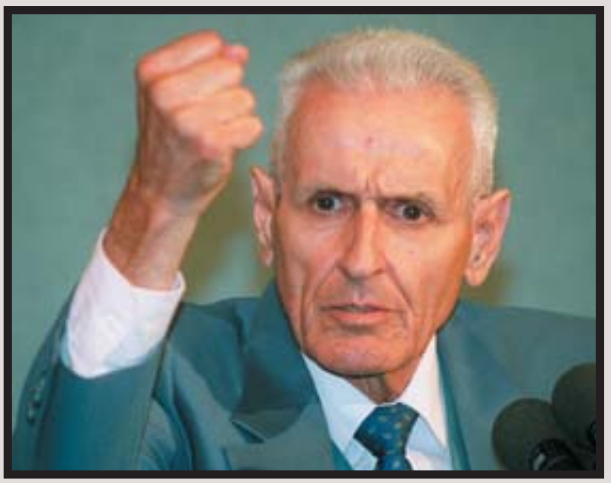
All three of these skills, by the way, are the ones affected in childhood disorders such as attention-deficit hyperactivity disorder. It is easy to see how the notion of old age as a second childhood developed—and how age-related brain deficits may one day be treated in much the same way.

There are reams of evidence that old people who stay in touch with family, friends, church and society stay in better shape physically and mentally. Data even show that an active social life benefits brain function as much as physical fitness does. Staying socially active also helps to maintain a positive attitude, by improving feelings of self-worth. One study revealed that older adults who attended religious services at least once a week had a survival advantage over those who did not attend. Whether it was the activity or a spiritual boost, the message is clear: you've got to stay engaged.

A RIGHT TO DIE?

Advocates of the right to die—as well as journalists covering the issue—routinely raise the horrors of old age as an argument in favor of assisted suicide, championed by Jack Kevorkian, a retired pathologist who is now serving a related 10- to 25-year prison sentence. But oldness, like beauty, is in the eye of the beholder. Although an 80-year-old woman might look miserable to a middle-ager, she is most likely to compare herself to a 90-year-old—and to conclude that she is doing reasonably well.

This positive outlook is a standard feature of human psychology. Even major illness and loss cannot put a dent in an ordinary person's sense of well-being for more than a few years. In study after study, victims describe themselves as being as happy overall as they were before their trauma.



ASSISTED SUICIDE CRUSADER: Jack Kevorkian.

WILFREDO LEE *AP Photo*

The trick to happiness may be social contact. Researchers have found that a sick or disabled senior who is surrounded by friends and family will tend to characterize his or her life as satisfactory. Studies by Joel Tsevat of the University of Cincinnati Medical Center found that 43 percent of his subjects in the worst physical condition and 51 percent with severe pain described their quality of life as good. In short, no one can divine an old person's state of mind by looking at the state of his or her body.

It is a slippery slope from believing in assisted suicide to simply assuming that a sick old friend or relative wants someone to help him or her die. Older Americans, who have a strong collective voice in politics and culture, should be allowed to speak for themselves. —*C.J.*

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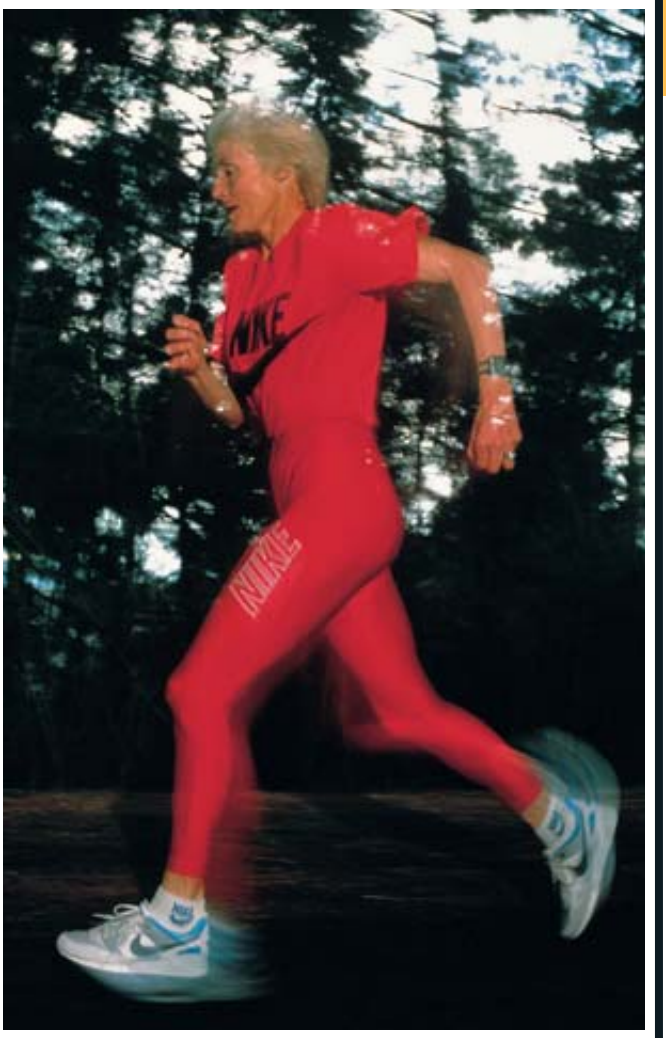
Elderly people who simply cannot get around may find help from the Internet. An aged person who can no longer walk or drive might be cheered by keeping up with friends and family through exchanging e-mail, electronic photos and online chats.

Perhaps the most critical act in maintaining plasticity is mental exercise. As Scheibel points out, mental exercise keeps the brain alive: "We now realize, through some very exhaustive work, that the so-called aging brain is just as powerful in learning as younger brains. The old phrase 'You can't teach an old dog new tricks' is simply not true."

Indeed, mental challenges, from crossword puzzles to political debates with friends, keep neuronal connections strong, just as physical exercise keeps muscle fibers strong. The "workout" lesson is the same: use it or lose it. Undertaking new hobbies, vocations or intellectual pursuits can help even further. Learning in old age may take a little longer, Scheibel says, but we remain potential learners our entire lives.



USE IT OR LOSE IT: Physical exertion helps to keep the brain supple; mental exercise keeps it sharp.

More exact advice on how to preserve mental health will surely expand as millions of baby boomers gray. Elkhonon Goldberg, clinical professor of neurology at New York University, has developed a program for normally aging baby boomers and the elderly that is designed to halt cognitive decline. Clients take an initial battery of neuropsychological tests and are assigned software programs to remediate their weaknesses. They then spend an hour working with their programs, two or three times a week. The results are encouraging, with most people showing modest but measurable gains in cognitive function. They report feeling "smarter," and many notice a drop in quick-wittedness after they've been away on vacation. "The program seems to contribute to a feeling of mental sharpness and lucidity," Goldberg says, although he emphasizes that "without running a very large-scale double-blind controlled study, there's no way to know for sure." The sheer numbers of aging men and women will change everyone's view of what old age can and should be. Robust mental health will be seen as an entitlement, not the minor miracle it is today. As a result, a significant segment of medicine will change.

"Geriatrics as a specialty is only 20 or 25 years old—there was such a small clientele until 30 years ago," Scheibel says. "And research interest in aging goes back only another 15 years before that."

At the social level, retirement will change substantially or be done away with. Scheibel himself exemplifies the trend: forced retirement has been abolished in the University of California system, and he has continued to teach and conduct research at U.C.L.A. He believes that the social custom of retirement may itself be responsible for the loss of frontal-lobe function that we now accept as normal. He notes that studies at the University of California at Berkeley by his wife, Marian Diamond, show that "if you stimulate [brain function] you keep it; if you don't, you lose it. One of the worst things we did for high-achieving people was to make them retire. Now we're developing legislative acts to reject this."

At 81, Scheibel is a committed optimist. "In most cases," he says, "aging brings about wisdom." The growing ranks of elderly, he feels, will be "like having a vastly expanded senate in our civilization." We humans will not go gently into a 30-year state of disability and despair. Once we know what the problems are going to be, we will do our best to figure out how to thrive. SA

Catherine Johnson, based in Irvington, N.Y., is co-author with John Ratey of Shadow Syndromes *(Pantheon, 1997).*

MORE TO EXPLORE

Why Zebras Don't Get Ulcers. Robert Sapolsky. W. H. Freeman and Co., 1998.

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ED KASHI

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ESSAY

No Truth to the Fountain of Youth

Fifty-one scientists who study aging have issued a warning to the public: no antiaging remedy on the market today has been proved effective. Here's why they are speaking up

By S. Jay Olshansky, Leonard Hayflick and Bruce A. Carnes

Illustrations by J. W. Stewart

Efforts to combat aging and extend human life date at least as far back as 3500 B.C., and self-proclaimed experts have touted antiaging elixirs ever since. Indeed, the prospect of immortality has always had universal appeal, spurring Alexander the Great and Ponce de León to search for the legendary Fountain of Youth and feeding alchemists' desire to manufacture gold (once believed to be the most potent antiaging substance in existence). But the hawking of antiaging "therapies" has taken a particularly troubling turn of late. Disturbingly large numbers of entrepreneurs are luring gullible and frequently desperate customers of all ages to "longevity" clinics, claiming a scientific basis for the antiaging products they recommend and, often, sell. At the same time, the Internet has enabled those who seek lucre from supposed antiaging products to reach new consumers with ease.

Alarmed by these trends, scientists who study aging, including the three of us, have issued a position statement containing this warning: no currently marketed interven-

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tion—none—has yet been proved to slow, stop or reverse human aging, and some can be downright dangerous. While the public is bombarded by hype and lies, many biologists are intensively studying the underlying nature of aging in the belief that their research will eventually suggest ways to slow its progression and to thereby postpone infirmity and improve quality of life. But anyone purporting to offer an antiaging product today is either mistaken or lying. The full position statement, drafted and endorsed by 51 internationally recognized investigators, can be found on the *Scientific American* Web site [*see bottom of page 102*]. Here we state the case as we see it, speaking for ourselves.

What Aging Is ... and Isn't

ANY DISCUSSION OF AGING should first clarify its terms. Various definitions have been proposed, but we think of aging as the accumulation of random damage to the building blocks of life—especially to DNA, certain proteins, carbohydrates and lipids (fats)—that begins early in life and eventually exceeds the body's self-repair capabilities. This damage gradually impairs the functioning of cells, tissues, organs and organ systems, thereby increasing vulnerability to disease and giving rise to the characteristic manifestations of aging, such as a loss of muscle and bone mass, a decline in reaction time, compromised hearing and vision, and reduced elasticity of the skin.

This accretion of molecular damage comes from many sources, including, ironically, the life-sustaining processes involved in converting the food we eat into usable energy. As the energy generators of cells (mitochondria) operate, they emit destructive, oxidizing molecules known as free radicals. Most of the damage caused by these reactive molecules gets repaired, but not all. Biologists suspect that the oxidative assaults ultimately cause irreparable injury to the mitochondria, thereby impeding a cell's ability to maintain the integrity of the countless molecules needed to keep the body operating properly. The free radicals may also disrupt other parts of cells directly.

Aging, in our view, makes us ever more susceptible to such ills as heart disease, Alzheimer's disease, stroke and cancer, but these age-related conditions are superimposed on aging, not equivalent to it. Therefore, even if scientific advances could eliminate today's leading killers of older individuals, aging would continue to occur, ensuring that different maladies would take their place. In addition, it would guarantee that one crucial body component or another—say, the cardiovascular system—would eventually experience a catastrophic failure. It is an inescapable biological reality that once the engine of life switches on, the body inevitably sows the seeds of its own destruction.

Men and women in the developed world typically live longer now (75 and 80 years, respectively) than they did throughout much of history (about 25 years) because human ingenuity—which brought us sanitation systems, vaccines, antibiotics and so on—has had phenomenal success in thwarting the infectious and parasitic diseases responsible for a great deal of premature death. We live longer now not because we have altered the way we age but because we have altered the way we live.

Though inevitable, aging is not, as some might think, a genetically programmed process, playing itself out on a rigidly predetermined time schedule. The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live. Just as an automobile does not have a built-in plan for decline written in its blueprints, we do not possess genetic instructions that tell our bodies how to age or when to die.

The primary goal of biomedical research and efforts to slow aging should not be the mere extension of life. It should be to prolong the duration of healthy *life.*

The logic behind this assertion goes basically like this: Genes perpetuate themselves by orchestrating the transformation of a fertilized egg into a sexually mature adult that produces offspring. Clearly, any genetic variant that compromises this developmental process would be self-eliminating. Conversely, evolution is totally blind to the consequences of gene action (whether good, bad or indifferent) after reproduction is achieved. Genes or genetic variants that prove detrimental in the postreproductive part of the life span can become commonplace, but only if they participate in important processes early on. For example, several genes that contribute to cancer in the later years are known to participate in

THE AUTHORS

S. JAY OLSHANSKY, LEONARD HAYFLICK and *BRUCE A. CARNES* have all studied aging for many years and spearheaded the drafting of the position statement on aging discussed in this essay. Olshansky is professor of public health at the University of Illinois at Chicago. Hayflick is professor of anatomy at the University of California, San Francisco. Carnes is associate professor in the department of geriatric medicine at the University of Oklahoma Health Sciences Center.

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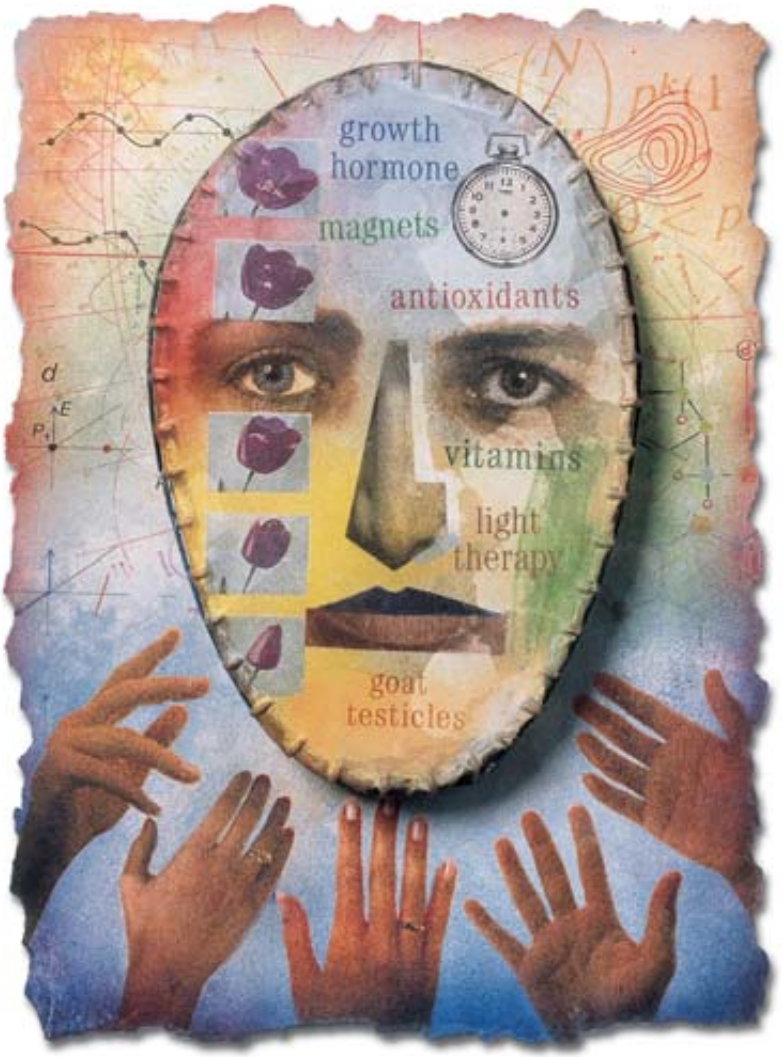
growth and development early in life.

Without a doubt, a host of our genes influence aging, but they do so indirectly, as an inadvertent by-product of processes involved in growth, development, and the maintenance of health and vigor. The lack of a specific genetic program for aging and death means that there are no quick fixes that will permit us to treat aging as if it were a disease. A single genetic intervention in an organism as complex as a human being would have little chance of combating the probably vast array of genes and biological activities that play subtle, unpredictable parts in the timing of our ultimate demise.



False Claims

DESPITE THIS COMPLEXITY, some researchers believe that they may manage to find ways to slow the rate of human aging. If they succeed, many people will live longer than would otherwise be expected, and a few people might even surpass the modern longevity record of 122 years. But the primary goal of biomedical research and efforts to slow aging should not be the mere extension of life. It should be to prolong the duration of healthy life. Slowing the rate of aging could help postpone the onset of age-related diseases and infirmities, essentially enabling people to stay younger longer.

On what grounds do we assert so vehemently that no purported antiaging intervention has been proved to modify aging? To assess whether an intervention has affected a biological process, researchers need a yardstick for measuring that process. In this case, no single or aggregate age-related phenomenon has proved to be a reliable indicator of the rate of aging in humans or other species. Without a yardstick, there can be no measurements, and without measurements there can be no assurance that an intervention was successful.

People eager to retain or restore their youthful biology might well recognize the paucity of proof but decide to try a putative antiaging intervention anyway, thinking they have little to lose. They should think again. For instance, the U.S. Food and Drug Administration does not require products that are sold as dietary supplements to undergo the rigorous tests of safety and effectiveness that medicines must pass before they can be sold to the public. Consequently, these supplements come with no guarantees of purity or potency, no established guidelines on dosage, and often no warnings about side effects that may result when the products are taken along with approved medications.

Antioxidants constitute one popular class of supplements touted to have antiaging powers. Such chemicals occur naturally in the body and in fruits and vegetables and are believed to neutralize free radicals. Proponents claim that if taken in sufficient quantities, antioxidant supplements will sop up the radicals and slow down or stop the processes responsible for aging. But eliminating all free radicals would kill us, because they perform certain necessary intermediary steps in biochemical reactions. Further, although epidemiological studies have demonstrated that the antioxidant vitamins E and C contained within the foods we eat may reduce the risk of cancer, macular degeneration and other disorders, no one has established that vitamin supplements containing antioxidants limit oxidative damage in the body or influence aging.

Like antioxidants, another fashionable antiaging intervention, hormone replacement, has a plausible rationale. This strategy was first popularized early in the 20th century, when older men occasionally submitted to the grafting of testicles from goats or monkeys or received in-

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jections of macerated testicles. Today pure forms of hormones can be administered. The replacement strategy seems logical in principle because the blood levels of most hormones—among them melatonin, growth hormone, testosterone and dehydroepiandrosterone (DHEA)—commonly decrease with age. Also, experiments on older men have demonstrated that some physical and physiological attributes that show declines over time, notably muscle mass and skin elasticity, respond favorably in the short term to growth hormone replacement.

On the other hand, hormones can cause worrisome side effects. In mice, for instance, delivery of melatonin increases the risk of tumor development, and the overproduction of growth hormone leads to kidney problems, premature heart and lung failure, and an increased probability of early death. Human adults given growth hormone have suffered from acromegaly (excess bone growth) and carpal tunnel syndrome. Estrogen replacement therapy may offer health benefits to some postmenopausal women; however, this form of therapy has recently been challenged and has risks of its own, such as breast cancer and blood clots. In short, hormone replacement therapy has a place in the treatment of specific age-associated disorders, but evidence that it affects the rate of aging is lacking.

People might well recognize the paucity of proof but decide to try a putative antiaging intervention anyway, thinking they have little to lose. They should think again.

Some people might wonder whether following today's public health recommendations for diet and exercise can serve as a more natural Fountain of Youth. Good nutrition and regular exercise do reduce the risk of various diseases and, in that way, may extend the duration of life for many people—thereby serving as the best current prescription for a long and healthy life. As is true of other interventions, though, no one has shown that diet or exercise, or both, directly influences aging.

What Science Says

WE FIND IT IRONIC that a phony antiaging industry is proliferating today, because serious efforts to understand aging have advanced greatly in recent years. Biologists who work with yeast, roundworms, fruit flies and mice have extended life by manipulating the genes of those species. These genetic alterations did not affect what is believed to be an important hallmark of aging in a population (an exponential increase in the risk of dying with time after puberty), which means that the longevity extensions in those experiments cannot safely be interpreted as resulting from an intervention in the aging process. Nevertheless, further study of those genes could offer clues to the influences on longevity and to approaches that might postpone infirmity and age-related disorders.

Another avenue of research may also lead to true aging interventions. Investigators have known for decades that caloric restriction extends life and the duration of good health in all species in which it has been studied, as long as the diet includes enough nutrition for routine maintenance of the body. These findings suggest that caloric restriction might have similar effects in humans. Given that few people would ever reduce their food intake enough to lengthen their lives, biologists are now trying to discover the mechanism that underlies the benefits of caloric restriction and to find agents that might mimic those helpful effects in people without forcing them to go hungry.

A number of scientists look at current research trends and feel hopeful. They can envision a time when treatments based on an understanding of aging can help slow its progression and when not yet specialized (stem) cells can be coaxed to repair and rejuvenate damaged tissues, enabling people to remain vigorous longer than they would without medical assistance. Not all researchers share that optimism, though. Some assert that aging's complexity will forever militate against the development of antiaging therapies.

One thing is indisputable: the number of elderly people is growing worldwide, and opportunists stand ready to cash in on the burgeoning market for antiaging products. The researchers who wrote and endorsed the position paper appearing on *Scientific American*'s Web site do not necessarily agree on every word written there, but everyone realized that we had to set aside our minor differences to raise awareness of the growing scam. The public needs to know that the products sold as antiaging remedies at longevity clinics and elsewhere have no scientifically proved efficacy and may at times be harmful. Systematic investigations into aging and its modification are in progress and could one day provide methods to slow our inevitable decline and extend health and longevity. That day, however, has not dawned yet. SA

MORE TO EXPLORE

The Aging of the Human Species. S. Jay Olshansky, Bruce A. Carnes and Christine K. Cassel in *Scientific American,* Vol. 268, No. 4, pages 46–52; April 1993.

The full position statement on aging and its extensive references can be found at **www.sciam.com/agingstatement.cfm**

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